TABLE 1. *Summary of Data on All Cases.*

CASES WITH NORMAL INITIAL PROTHROMBIN LEVELS							CASES WITH LOW INITIAL PROTHROMBIN LEVELS								
CASE NO.	PROTHROMBIN LEVEL	HIPPURIC ACID EXCRETION	BROMSULFALEIN RETENTION		UROBILINOGEN EXCRETION	REMARKS	CASE NO.	PROTHROMBIN LEVEL			HIPPURIC ACID EXCRETION	BROMSULFALEIN RETENTION		UROBILINOGEN EXCRETION	REMARKS
			5 min.	15 min.				Before treatment	After treatment	Change		5 min.	15 min.		
	%	gm.	%	%	posit. dil.			%	%	%	gm.	%	%	posit. dil.	
CHRONIC HEPATITIS (CIRRHOSES)															
3	100	2.0	70	20	32		1	52	56	+4		80	5	64, 128	
4	100	2.0	90	20	2		2	30	50	+20	1.2	65	60		
26	100	2.5	40	15	16		5	24	40	+16	2.6	60	40	256, 32	
29	100	1.3	55	10			6	50	50	0	1.4	100	85	4	
30	100	1.0	30	10			7	45	51	+6	0.1			128, 64	
33	90	1.4	100	30	64, 64		8	50	40	−10				64, 128	Patient died
34	**95**	**1.5**	**70**	**15**	**256, 64**	Patient died	9	45	46	+1				5 mg.*	
35	**100**	**0.4**	**80**	**65**	**16**	Patient died	10	27	32	+5	1.1	100	90	40, 80	
39	80	Low	100	50	2.8 mg.*		11	30	39	+9	0.8	100	45	32, 64	
40	81	1.7	40	5	16	Patient died	12	50	33	−17	1.5	80	40	16, 16	Patient died
41	90	2.5	50	5	128		27	44	39	−5	1.7			64, 32	
42	100	0.9					28	60	48	−12	2.0			256	Patient died
44	100	1.1			32		31	48	45	−3	1.7			64, 128	
46	100	0.6			256, 32		32	43	70	+27	2.0	35	15	128, 2	
48	80	1.0					36	45	60	+15	1.4			32, 512	Patient died
50	90	2.0	60	45	16, 16		43	54	60	+6	0.7			256, 64	
51	100	2.3			4		45	70	78	+8	Low	100	5	32	
52	100	0.5	60	35			47	30	62	+32	0.5			32, 4	
54	100	1.6					49	38	33	−5	1.0	90	45	8	Patient died
66	100	2.0	70	10	128, 64		53	50	90	+40†	1.4	50	30	0	
67	100	1.4	80	65	64, 64		55	28	37	+9	0.3	90	60	32, 128	Patient died
77	98	1.3	50	30	128, 32		90	65	70	+5†	2.5	15	10		
83	100	0.5	100	95			91	62	68	+6	3.8	5	Tr.	16, 4	
84	80	3.6					94	40	40	0	1.1				
86	80	1.6	35	10	128		95	40	40	0	1.2				
92	96	2.7					97	60	60	0	1.3				
100	100	2.0	40	25			98	65	65	0	1.0				
ACUTE HEPATITIS															
56	100	1.0	100	45	64, 16		14	42	23	−19	0.7			0, 0	Patient died
57	100	2.0			8, 8		15	35	80	+45	1.7	100	80	64, 16	
61	98	1.1			8, 16		16	40	100	+60		90	60	4, 0	
85	82	0.5	10	0		Patient died	17	68	29	−39	1.3			0, 64	Patient slowly recovered
							24	32	100	+68	1.5	65	40	0, 4	
							58	30	100	+70	1.1	20	5	32, 16	
							59	52	100	+48	2.8	40	10	0, 32	
							60	56	80	+24	1.3				
							87	71	95	+24	0.4				Patient died
							88	40	23	−17	1.3			2, 1	Patient died
							93	20	23	+3	0.7				
							96	36	40	+4	1.3				
OBSTRUCTION OF COMMON DUCT															
38	80	1.6			32	Cancer	18	60	62	+2				0	Cancer
64	100	1.4			32, 32	Gallstone	19	75	100	+25	0.4			2	Cancer; patient died.
65	100	2.0			4, 0	Cancer									
68	85	1.2			80, 0	Cancer	20	45	100	+55	1.4			0	Cancer
69	95	1.2			0	Cancer	21	15	100	+85	2.0	85	30	0	Adhesion
							22	20	100	+80				2, 2	Stricture
							23	20	100	+80	1.0	100	80	8	Stricture
							25	16	73	+57	0.8			128, 0	Stricture; patient died.
							62	24	39	+15	1.5				Cancer
							99	30	100	+70	0.4			0	Cancer
TUMORS OF LIVER AND SO FORTH															
13	88	4.2	20	5		Hodgkin's disease	76	67	70	+3‡	1.3	30	20	16, 4	Cancer; patient died.
37	100	1.7	100	80	128	Cancer; patient died.	80	70	99	+29	1.1				Cancer; patient died.
63	100	2.8				Blood dyscrasia	81	31	100	+69	1.3	30	Tr.		Hodgkin's disease
75	100	0.5			16	Cancer									
78	86	2.0			8, 0	Cancer									
79	100	2.5				Cancer									
82	98	0.3				Cancer; patient died.									
89	92	2.2	20	5	8	Cancer ?									
GALL-BLADDER DISEASE															
70	100	1.1	30	15	128		71	44	53	+9		40	20	32	Patient died
73	100	2.6					72	78	87	+9	2.1				
74	100	2.8													

*Watson test.

†After three weeks.

‡After two weeks.

The prothrombin level remained below normal after treatment in 35 cases. Twenty-five were cases of chronic hepatitis, and 1 was a case of common-duct stone with biliary cirrhosis. In 5 cases of acute hepatitis, 3 patients died, and 2 made slow recoveries. There was 1 case of cancer of the liver, 3 of obstructive jaundice due to cancer of the head of the pancreas, and 1 of cholecystitis, with postoperative bronchopneumonia and abscess of the lung.

TABLE 2. *Number of Cases with Abnormal Tests before and after Treatment.*

DIAGNOSIS	NO. OF CASES	HIPPURIC ACID EXCRETION		PROTHROMBIN LEVEL	
		BEFORE	AFTER	BEFORE	AFTER
Chronic hepatitis	54	45	40	27	25
Acute hepatitis	16	15	10	12	5
Obstruction	14	13	11	9	3
Tumors and so forth	11	8	8	3	1
Gall-bladder disease	5	2	2	2	1
	100	83*	71	53	35

*In 8 cases, no oral hippuric acid test could be performed.

Diagnosis

Table 1 shows all the cases in which the initial prothrombin level was below normal. The initial prothrombin values and those found after three or four days of treatment with vitamin K are given, as well as the net change in the prothrombin level during that period. The initial prothrombin level was similar in the three groups,—obstructive jaundice, acute hepatitis and chronic hepatitis,—but the response to treatment with vitamin K was very different.

In the obstructive cases, the initial prothrombin level was below normal in 8 of 14 cases and, as a rule, rose quickly to normal in one to three days. In the cases of acute hepatitis, the prothrombin level rose rapidly to normal in the majority of cases, possibly because the tests were made at the time recovery began. In 2 fatal cases (Cases 14 and 88), the prothrombin level fell. In 1 (Case 17), the prothrombin fell at first and slowly returned to normal. In 1 (Case 87) of acute liver necrosis due to carbon tetrachloride poisoning, the prothrombin gradually rose to normal, but the patient died later of septicemia with metastatic abscesses.

The 27 cases of chronic hepatitis with an initial low prothrombin level behaved quite differently from those in the other two groups. After treatment, there was a well-marked rise in only 2 or 3 cases; in 13, there was a slight rise; in 5, there was no change; and in 6, 4 of which were fatal, the level fell. In most of these cases, the prothrombin remained at a distinctly low level of about 40 to 50 per cent after vitamin K therapy, which is quite unlike the first two groups, in which the level rose to normal except in a small percentage of cases (Table 1).

Correlation of Visible Bleeding with Prothrombin Levels

In the whole group, there were 6 cases of visible bleeding associated with low prothrombin levels (5, 20, 23, 27, 30 and 35 per cent): 1 case of bleeding from the nose and gums, 2 of ecchymosis, 1 of hematuria, 1 of hematuria and bleeding from the nose and gums, and 1 of hemoptysis. Pohle and Stewart[10] found 10 such cases (7 per cent) among 136 cases of liver and biliary-tract disease.

It is interesting to note that there were 15 other cases with low prothrombin levels (10, 15, 16, 23, 24, 27, 28, 29, 29, 30, 30, 30, 31, 32 and 35 per cent) and no visible bleeding. Pohle and Stewart found 15 such cases (11 per cent) in their group of 136 cases.

There were 8 other cases of bleeding with normal prothrombin levels; 4 cases of gross hematemesis, 1 of melena that was probably due to varices in cirrhosis, 2 of epistaxis, and 1 of melena with cancer of the rectum.

COMMENT

Methods. The variation in methods for performing the hippuric acid excretion test by the gravimetric method may account for the different normal values cited by various authors. Our experience and that of Snell and McGrath[21] and of Quick[15] show that the greatest number of normal tests with the method used have ranged between 2.5 and 3.5 gm., with occasional values at 4 and 5 gm. When hippuric acid crystals in the urine are subjected to the additional procedure of salting out, as suggested by Weichselbaum and Probstein[22] and later by Quick,[23] the majority of normal values fall in the higher range.

A confusing factor in prothrombin determination is due to the fact that some workers use the initial prothrombin percentage and others the response to vitamin K analogues. The latter seems to be the better criterion, since the variable factor of adequate vitamin K is ruled out. Moreover, the initial figures do not have any possible differential value.

After performing a large number of prothrombin tests and correlating them with clinical observations, we considered a value of 80 to 100 per cent to be within normal limits. When the time of the unknown was shorter than the normal control, the value was recorded as 100 per cent.

Acetone extracts of whole rabbit brain, even in dilution, gave no constant value that could be du-

plicated and therefore were considered unsatisfactory.

Blood collected for this determination should not be allowed to stand for more than four hours, because fibrinogen is precipitated and is a definite source of error.

The curve shown in the paper by Kark and Lozner[16] was used in converting coagulation time to prothrombin per cent.

Dilution of the plasma for the prothrombin test may be a source of error.

Correlation of tests. It is obvious that the degree of correlation between the two tests is very poor, and that the prothrombin test does not discover the milder grades of liver damage but only those that are well marked. The prothrombin level was abnormal in only 53 per cent of the cases; it may be normal when liver damage is well marked and readily shown by other tests. This agrees with the work of DeLor and Reinhart[24] and of Lucia and Aggeler.[14]

Prognosis. The prognostic value of an increased prothrombin level after treatment is definite but limited in scope. In diseases of the liver after adequate treatment with vitamin K, several types of response occur. The prothrombin level may return to normal within twenty-four to forty-eight hours in some patients, or may rise gradually over a period of weeks. In other cases, it may fail to rise or may actually fall despite adequate therapy. In cases in which after vitamin K treatment the prothrombin level rises only a little, fails to rise or falls, the prognosis is progressively poorer. A falling prothrombin level with adequate vitamin K therapy usually means irreversible damage to the liver and corresponds quite well with low hippuric acid test values. All 4 patients in whom this occurred died within a short time.

On the other hand, in the cases in which the prothrombin percentage returns to normal, the test is a much less accurate guide in prognosis than the hippuric acid excretion, since the prothrombin level may become normal or approximately normal in the presence of serious disease of the liver. Four patients — 2 with cancer of the liver, 1 with cancer of the pancreas, and 1 with acute hepatitis with multiple abscesses — died within a week after normal prothrombin determination. The hippuric acid test was very low in all. This is entirely in agreement with Quick's[25] recent statement that good liver function and a low prothrombin level are better from the patient's point of view than poor liver function and a high prothrombin level.

In estimating the risk at operation in diseases of the liver and biliary passages, the prothrombin level is the best guide to the presence of a bleeding tendency, but the hippuric acid excretion has proved much better than the prothrombin percentage in revealing general hepatic insufficiency.

In cirrhosis, the prothrombin level may not respond well to treatment, but the percentage of normal prothrombin can be kept well above the bleeding level. Bleeding in the hepatic cirrhoses

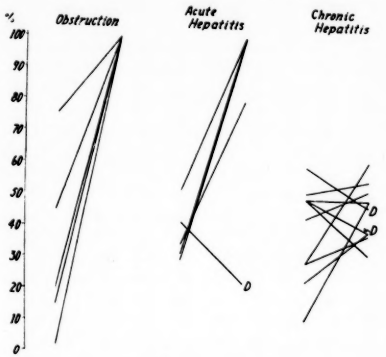

FIGURE 1. *Early Prothrombin Response to Vitamin K Treatment in 20 Cases.*

was about as often due to ruptured varices as to a low prothrombin level in our experience.

In one patient with cirrhosis, the prothrombin percentage remained low after injections of naphthoquinone derivatives, and a poor prognosis was given, but proved to be an error. When this patient was seen a year later, after much restriction in the use of alcohol and a more normal diet, the prothrombin level was found to be 100 per cent of normal, but the hippuric acid and bromsulfalein excretion was definitely diminished.

In short, in response to vitamin K treatment in the patient with a relatively good liver function (early obstruction), or with a recovering liver (acute hepatitis), the prothrombin level returned rapidly to normal; with severe chronic damage (chronic hepatitis), the prothrombin level remained relatively low.

A small number of cases of acute hepatitis with low initial prothrombin percentage showed rapid increase to normal, after the use of increased amounts of glucose and fluids and without the aid of vitamin K analogues. It has been suggested that glucose plays a vital role in blood coagulation.[26]

Fatal cases. The prothrombin levels were low a few days to a week before death, in spite of ac-

tive treatment with vitamin K, in 7 cases with an acute element: 2 of acute hepatitis (prothrombin levels of 10 per cent), 4 of acute exacerbations in chronic hepatitis, and 1 of cholecystitis with an acute lung abscess (32, 40, 48, 48 and 53 per cent, respectively).

The prothrombin levels were low in 4 other cases tested one to two months before death: 2 of cardiac cirrhosis and 2 of portal cirrhosis (23, 33, 28 and 42 per cent, respectively).

The levels were high or normal within a week of death in 4 cases: 3 of cancer of the liver and 1 of cancer of the pancreas (70, 80, 98 and 100 respectively).

The levels were also high in 6 cases tested one month before death: 3 of cirrhosis, 1 of pylephlebitis and 2 of cancer of the liver (81, 90, 90, 95, 100 and 100, respectively).

In contrast to these results, the hippuric acid was always low or very low in fatal cases tested within a week of death (0.3, 0.3, 0.4, 0.7, 1.2, 1.3, 1.7 and 2.0 gm.), and was low in every fatal case but one (cardiac cirrhosis) tested one to two months before death (0.3, 0.4, 1.5, 1.7 and 2.0 gm.).

Diagnosis. The prothrombin level has some suggestive value in differential diagnosis of diseases of the liver, but the results must be interpreted with some degree of caution. One feature stands out: a prompt return to normal after vitamin K treatment has been found more commonly in obstructive jaundice than in some types of parenchymal damage, but a sharp distinction must be made between acute and chronic forms of the latter.

Andrus[12] has emphasized the value of prothrombin tests in the study of liver function. He states:

> The [prothrombin] test finds one of its greatest fields of usefulness in distinguishing between jaundice of extrahepatic origin due, for example, to obstruction of the common duct by tumor or stone and that due to parenchymal liver disease. In brief, we have found that in the former, the plasma prothrombin either remains above 80 per cent or if it be depressed, rises following the intramuscular injection of 2-methyl-1, 4-naphthoquinone by more than 10 per cent in the first forty-eight to seventy-two hours. In intrahepatic jaundice the prothrombin, which here is uniformly depressed, either fails to rise by this amount or continues to fall.

In 40 jaundiced patients, — 25 with common-duct obstruction and 15 with parenchymatous liver disease, — he found the test to be almost 100 per cent correct.

An effort was made to use this rapid type of response to vitamin K treatment as an aid in the diagnosis of obstructive jaundice. In 4 cases of severe jaundice with acholic stools for a period of one or two weeks, in which the diagnosis of obstruction was seriously considered, there was an immediate rise to normal in the prothrombin level on vitamin K therapy; however, all these cases were proved to be acute parenchymatous hepatitis by an unmistakable course and subsequent history.

In our 14 cases of obstructive jaundice, there were 9 (64 per cent) with low initial prothrombin levels. The percentage of such cases has been higher in other reported series — Stewart and Rourke[9] found 80 per cent in 24 cases, and Pohle and Stewart[27] 87 per cent in 23 cases.

The presence or absence of urobilinogen in the urine and feces has proved to be the most valuable differential test between completely obstructive and parenchymatous jaundice. The hippuric acid and bromsulfalein tests have no differential diagnostic value, since they are positive in nearly every case of liver disease, regardless of its type.

Summary

The blood prothrombin level and its response to vitamin K treatment were compared with standard liver-function tests, such as the hippuric acid and fractional bromsulfalein excretion, and the urobilinogen in the urine in a group of 100 cases of various diseases of the liver, and although of prime value in revealing vitamin K deficiency, was found to be of secondary importance as a liver-function test.

The degree of correlation between the prothrombin level and the liver-function tests used was very poor. The prothrombin test does not reveal the milder grades of liver damage but only those that are well marked. It was abnormal in only 53 per cent of the cases, and may be normal when liver damage is well marked and easily shown by the other tests.

The prothrombin level was less definite in prognosis than the liver-function tests used (with the single exception of discovery of a bleeding tendency). If normal, it may be misleading. An abnormal test is significant, and if a low prothrombin level rises but little, fails to rise or falls after vitamin K treatment, the prognosis is progressively unfavorable. In acute hepatitis, a falling prothrombin level in the presence of adequate vitamin K usually means irreversible, widespread liver damage.

In differential diagnosis of diseases of the liver, the prothrombin level has only a suggestive and limited value. The sole diagnostic point noted is that the prothrombin percentage is much likelier to rise rapidly to normal after vitamin K treatment

FRANKLIN SQUARE HOSPITAL LIBRARY

in obstructive jaundice and healing acute hepatitis than in chronic hepatitis (cirrhoses).

In some cases of acute hepatitis with low initial prothrombin levels, there has been a rapid response to active glucose and fluid intake comparable to that in similar cases treated with vitamin K.

Bleeding in the hepatic cirrhoses was about as frequently due to ruptured varices as to a low prothrombin level.

The authors acknowledge their indebtedness to Dr. Robert Kark, formerly research fellow in medicine, Harvard Medical School, for prothrombin data in some of the earlier cases, and to Miss Dorothy Jensen and Mr. William Appleby for technical assistance.

References

1. Quick, A. J., Stanley-Brown, M., and Bancroft, F. W. A study of the coagulation defect in hemophilia and in jaundice. *Am. J. M. Sc.* **190**:501-511, 1935.
2. Smith, H. P., Warner, E. D., and Brinkhous, K. M. Prothrombin deficiency and the bleeding tendency in liver injury (chloroform intoxication). *J. Exper. Med.* **66**:801-811, 1937.
3. Warren, R., and Rhoads, J. E. The hepatic origin of the plasma-prothrombin observations after total hepatectomy in the dog. *Am. J. M. Sc.* **198**:193-197, 1939.
4. Quick, A. J. Nature of the bleeding in jaundice. *J. A. M. A.* **110**:1658-1662, 1938.
5. Butt, H. R., Snell, A. M., and Osterberg, A. E. The preoperative and postoperative administration of vitamin K to patients having jaundice. *J. A. M. A.* **113**:383-390, 1939.
6. Warner, E. D. Discussion of Butt, Snell and Osterberg.[5]
7. Kark, R., and Souter, A. W. Synthetic vitamin K in treatment of hypoprothrombinaemia. *Lancet* **1**:1149-1153, 1940.
8. Wilson, S. J. Quantitative prothrombin and hippuric acid determinations as sensitive reflectors of liver damage in humans. *Proc. Soc. Exper. Biol. & Med.* **41**:559-561, 1939.
9. Stewart, J. D., and Rourke, G. M. Control of prothrombin deficiency in obstructive jaundice: by use of vitamin K. *J. A. M. A.* **113**:2223-2227, 1939. Prothrombin and vitamin K therapy. *New Eng. J. Med.* **221**:403-407, 1939.
10. Pohle, F. J., and Stewart, J. K. Observations on the plasma prothrombin and the effects of vitamin K in patients with liver or biliary tract disease. *J. Clin. Investigation* **19**:365-372, 1940.
11. Smith, H. P., Ziffren, S. E., Owen, C. A., and Hoffman, G. R. Clinical and experimental studies on vitamin K. *J. A. M. A.* **113**:380-383, 1939.
12. Andrus, W. DeW. The newer knowledge of vitamin K. *Bull. New York Acad. Med.* **17**:116-134, 1941.
13. Kark, R., White, F. W., Souter, A. W., and Deutsch, E. Blood prothrombin levels and hippuric acid excretion liver function test in liver disease. *Proc. Soc. Exper. Biol. & Med.* **46**:424-426, 1941.
14. Lucia, S. P., and Aggeler, P. M. The influence of liver damage on the plasma prothrombin concentration and the response to vitamin K. *Am. J. M. Sc.* **201**:326-340, 1941.
15. Quick, A. J. The synthesis of hippuric acid: a new test of liver function. *Am. J. M. Sc.* **185**:630-635, 1933.
16. Kark, R.,[2] and Lozner, E. L. Nutritional deficiency of vitamin K in man: a study of four non-jaundiced patients with dietary deficiency. *Lancet* **2**:1162, 1939.
17. Wallace, G. B., and Diamond, J. S. The significance of urobilinogen in the urine as a test for liver function: with a description of a simple quantitative method for its estimation. *Arch. Int. Med.* **35**:698-725, 1925.
18. Deutsch, E. A fractional bromsulfalein test to determine residual liver damage in the nonjaundiced patient. *New Eng. J. Med.* **225**:171-175, 1941.
19. White, F. W. The galactose tolerance and urobilinogen tests in the differential diagnosis of painless jaundice. *Am. J. Digest. Dis. & Nutrition* **4**:315-325, 1937.
20. White, F. W., Deutsch, E., and Maddock, S. The comparative value of serial hippuric acid excretion, total cholesterol, cholesterol ester, and phospho-lipid tests in diseases of the liver. I. The results of the tests. *Am. J. Digest. Dis.* **6**:603-610, 1939. II. A clinical comparison of the tests. *Ibid.* **7**:3-7, 1940.
21. Snell, A. M., and McGath, T. B. The use and interpretation of tests for liver function. *J. A. M. A.* **110**:167-174, 1938.
22. Weichselbaum, T. E., and Probstein, J. G. Determination of hippuric acid in urine. *J. Lab. & Clin. Med.* **24**:636-639, 1939.
23. Quick, A. J. Clinical application of hippuric acid and prothrombin tests. *Am. J. Clin. Path.* **10**:222, 1940.
24. DeLor, C. J., and Reinhart, H. L. An analysis of the hippuric acid, galactose tolerance, bromsulphthalein and prothrombin tests in 381 cases. *Am. J. Clin. Path.* **11**:617-622, 1940.
25. Quick, A. J. Discussion of Sharp, E. A. Vitamin K activity of 2-methyl-1, 4-naphthoquinone. *J. A. M. A.* **114**:439, 1940.
26. Tocantins, L. M., and O'Neill, J. F. Increased plasma prothrombin activity after epinephrine injections; relation to hyperglycemia. *Proc. Soc. Exper. Biol. & Med.* **47**:477-479, 1941.
27. Pohle, F. J., and Stewart, J. K. The cephalin-cholesterol flocculation test as an aid in the diagnosis of hepatic disorders. *J. Clin. Investigation* **20**:241-247, 1941.

FRACTURES AROUND THE ANKLE JOINT*

WILLIAM DARRACH, M.D.†

NEW YORK CITY

ANY pain or interference with the function of the ankle joint is a real handicap, whether the patient is a longshoreman, a clerical worker or a playboy. Injuries to this part of the body can be handled more intelligently and more successfully if the details of anatomy, physiology and pathology are understood and the general principles applied in each case than if a fixed rule of procedure is followed blindly.

Anatomy

The lower extremity of the tibia expands and becomes four sided. Its medial portion projects down as the medial malleolus. Articulating with the outer side is the expanded lower end of the fibula, which forms the lateral malleolus. The lower surface of the tibia is concave and articulates with the upper surface of the talus, which is narrower behind than in front and is in close contact on either side with the articular surface of the malleoli. The lower tibia and the two malleoli are spoken of as the mortise of the ankle, the talus being the tenon. The stability of the ankle, and indeed of the whole foot and leg, depends a good deal on the strength and accurate fitting of this tenon and mortise. It allows free flexion and extension, but no lateral motion; inversion and eversion of the foot take place in the subtalar and midtarsal joints. These three bones are held firmly in place by strong ligaments, which are also essential to stability. In front of and behind the adjacent margins of the lower tibiofibular joint are strong transverse bands, the anterior and posterior lower tibiofibular ligaments. In addition, and of vital importance, is the interosseous ligament. These three structures hold the lower ends of the tibia and fibula together and prevent a spreading

*Presented at the New England Postgraduate Assembly, Cambridge, Massachusetts, November 13, 1940.

†Professor of clinical surgery, Columbia University College of Physicians and Surgeons; attending surgeon, Fracture Service, Presbyterian Hospital, New York City.

of the mortise. The anterior and posterior tibiotalar ligaments are rather weak and of minor significance. The medial collateral ligament is a broad band passing from the under aspect of the medial malleolus forward, downward and backward in a fan-shaped manner, to be attached to the medial aspect of the talus, sustentaculum tali and adjacent surfaces of the navicular. It is a continuous sheet. On the outer side, the lateral collateral ligament is made up of three separate, distinct bands. The medial passes from the tip of the fibula to the outer surface of the os calcis, the anterior goes forward and inward to the body of the talus, and the posterior, which is the strongest, passes almost horizontally inward to the outer tubercle of the talus.

Mechanism of Injury

When undue strain is brought to bear on the ankle, various things happen. The medial malleolus may give way near its tip or at the base, or the medial collateral ligament may tear. On the outer side, one may find a similar tear of the ligament or lower transverse or higher oblique breaks of the lateral malleolus, or the fibula may give way in its lower shaft. If the strain on the mortise is too great, the lower tibiofibular ligaments may give way or, rarely, tear off a portion of the adjacent tibia. When the force is against the lower surface of the tibia, the posterior or anterior lip may give way.

Considering the problem from the standpoint of the causative factor, one finds that if the foot is overinverted the lateral malleolus may be pulled off, or the medial one pushed off, or the lateral collateral ligament torn. If the foot is everted, the medial malleolus or medial collateral ligament may give way, or the lateral malleolus may be forced off. If the latter holds, the lower tibiofibular ligaments give way. Rotation of the foot on the leg is apt to tear off the medial malleolus, or to give a high spiral fracture of the fibula. With compression, a tibial lip or an extensive comminution of the whole lower tibia may result. When the foot is forcibly driven backward, the wider anterior part of the talus spreads the mortise, and the malleoli or the interosseous ligament gives way.

In a few cases, one of these five forces — inversion, eversion, compression, rotation and backward thrust — may act alone, but usually several act together, especially in the severer injuries. If one enumerates the various combinations of lesions encountered in this region, the list becomes quite alarming. The classification that is useful from a practical standpoint of teaching, treatment and prognosis includes four main groups, with three other less common but serious varieties.

Types of Injury and Their Treatment

The first group comprises cases of fracture of either malleolus, without displacement and without gross ligamentous injury. These require no reduction, but a brief period (several days) of immobilization and elevation. A posterior molded plaster splint, removed for application of heat, massage and active motion, gives comfort. Weight bearing, with support, is allowed after seven to ten days. Full use is permitted in three to five weeks.

The second group differs from the first only in that there is displacement of the foot, which requires reduction and slightly longer immobilization. In addition to the posterior splint, a sugar tong or bilateral molded splint, to control the inversion and eversion, is used. Weight bearing is allowed about the fourth week.

In both groups, some cases show distinct evidence of marked joint swelling, with a good deal of pain made worse by any movement of the ankle. Relief of this pain can be obtained by aspiration of the joint. Removal of even 4 or 5 cc. of bloody fluid gives marked relief; as much as 15 cc. has been obtained. This should be carried out only with strict precautions, a small nick in the skin being made with a pointed knife and the needle inserted through this rather than forced through the skin.

The third group includes fractures of either malleolus, with tear of the opposite collateral ligament, or bimalleolar fractures with lateral or medial displacement of the foot, but without injury to the tibiofibular ligaments. Reduction is necessary. The foot must be brought into position under the leg, and one must hold the malleoli in place by molding the plaster splint carefully against and beneath the malleoli until the plaster has hardened. It is better to have the splints pass above the flexed knee, to control rotation. They may be shortened after two weeks. Weight bearing, with protection, is started after four weeks.

In the fourth group, — the true Pott's fractures, — in addition to a fracture of the medial malleolus or a tear of the medial collateral ligament, there is a high fracture of the fibula and, most important of all, a disruption at the lower tibiofibular joint. This results in an outward and posterior displacement of the foot on the leg. A satisfactory result depends on a satisfactory apposition of the normal relation, which should be maintained until the various injured structures have healed sufficiently to withstand the strain put on them.

After a careful study of x-ray evidence to determine just what the lesion is, the knee is flexed under anesthesia, to relax the gastrocnemius and to afford countertraction against the thigh. Steady,

LIBRARY
FRANKLIN SQUARE HOSPITAL

downward traction on the foot, the heel being held with one hand and the dorsum of the foot with the other, is gently and gradually applied with increasing force for several minutes. This usually overcomes the lateral displacement of the foot. The hand over the dorsum is then released and used to press backward on the tibia just above the ankle, forcing the foot forward on the leg. The thumb and fingers of the upper hand are used to approximate the malleoli, reducing the disruption of the lower tibiofibular joint. Splints are then applied by an assistant while the position is maintained by the operator, who shifts his hands in such a way as to maintain the traction and forward pressure of the foot, as well as the compression of the malleoli. This must be maintained until the plaster is sufficiently hard. With this type, it is necessary to maintain the immobilization for four to six weeks, although the knee can be mobilized at the end of two weeks. No weight bearing should be allowed for eight weeks, even with support. Disability lasts for three to four months or even longer.

Another type differs from the true Pott's fracture in that the fibula is not broken, but the main lesion is the disruption of the lower tibiofibular joint, with or without a fracture of the medial malleolus. This group is very important, because unless the diagnosis of disruption of the mortise is made and the treatment adjusted accordingly, the patient is very apt to have a permanent, marked disability. Unless firm union is obtained at this joint, the widened mortise leads to instability and persistent pain, which may last for years. If there is any doubt in the surgeon's mind, he should test the ankle under the fluoroscope to see if outward pressing of the foot tends to widen the mortise.

Another group includes cases of extensive comminution of the lower tibia, with any of the other lesions in addition. Accurate reduction can rarely be obtained by manipulation alone. Wire traction through the os calcis, with or without a second wire through the tibia above, sometimes accomplishes a fair reduction, but this type usually belongs in the operative class.

Another type is not a separate group, but includes fractures of either the posterior or the anterior lip of the tibia. The former is by far the commoner injury, and may be found as a complicating factor in any of the groups mentioned above.

Frequent failure to obtain or maintain satisfactory position in complicated ankle fractures, prolonged disability and the frequency of permanent disability have in recent years led me to put more of the severe types of ankle injuries into the operative class. By means of accurate, internal fixation, it has been possible to dispense with prolonged immobilization by splints and to start active motion a few days after the accident. I now believe that practically every disrupted lower tibiofibular joint should be operated on, and the two bones held in firm approximation by means of a transfixing bolt. In cases complicated by an anterior or posterior lip of the tibia or in comminuted cases, fragments can be realigned and held in position by screws, and small plates have frequently been used on the fibula. The results of this method have been most encouraging, and the disability time has been very markedly decreased.

As in any form of internal fixation of fractures, special technic, instruments and team training are essential, but if treatment is carried out with care, I believe that a great deal of time can be saved and permanent disability avoided.

The walking plaster boot is being used more and more. Certain precautions are indicated. This boot should be employed only when an accurate reduction has been obtained and maintained. It should be applied only after the primary swelling has subsided. Since the dependent position tends to increase congestion and swelling, the patient should be instructed to put his leg up at frequent intervals during the day. Sufficient cotton or sponge rubber should be placed between the sole of the foot and the plaster to lessen pressure. The boot must fit snugly beneath the expanding portion of the upper tibia. One disadvantage of this method is that it prevents the use of any heat, massage or active motions of the ankle. It is very useful, however, for patients who must be up and around for economic or other reasons.

* * *

Fractures around the ankle joint frequently result in a good deal of permanent disability and pain. If the cases are seen early and an exact evaluation of the various lesions is made by careful examination and thorough study of clear x-ray films, excellent reductions can usually be obtained in the first few hours. The method of splinting, the time of immobilization and the question of weight bearing should be determined by the probable length of time required for solid healing of the most serious lesion.

Widening of the mortise due either to disruption of the lower tibiofibular joint or to imperfect reduction is a most disabling affair. Disruption of the mortise can easily be overlooked, and should be searched for in each case. The operative treatment of the more complicated cases, in proper hands, will shorten the period of disability and improve the end results.

180 Fort Washington Avenue

HEREDITARY TELANGIECTASIS

Report of a Case

LAWRENCE I. STELLAR, M.D.*

BOSTON

HEREDITARY telangiectasis is a pathologic condition that occurs in and is transmitted through both sexes. The characteristic lesions — small red or purplish papules — occur in the mucous membranes, especially those of the upper respiratory and gastrointestinal tracts, in the skin and in some viscera. The papules consist of vessels made up of a single layer of endothelial cells and an abnormally thin epithelium. These vessels have a tendency to rupture, and thus give rise to bleeding. Hemorrhage has been reported most commonly in the form of epistaxis but, of course, may be seen elsewhere. The amount of blood loss tends to increase in later life.

The criteria for the diagnosis of this condition have been established by Goldstein[1] and affirmed by Larrabee and Littman[2] as follows: definite heredity, visible telangiectases, with pathologic distribution, and a tendency to bleed from the lesions.

According to Goldstein,[1] at the end of 1930, case reports of this condition involved about 550 members of 90 to 95 families. In spite of its rarity, hereditary telangiectasis should be thought of in the presence of bleeding; otherwise, the correct diagnosis may be missed or delayed. In the following case, the diagnosis was missed at each admission to the hospital.

CASE REPORT

C. G., a 56-year-old Canadian-born housewife, had been admitted several times to the Boston City Hospital.

From puberty on, she experienced recurrent nosebleeds preceding her menstrual periods. In 1928, she began to have severe nasal bleeding two or three times daily. Occasionally, the bleeding stopped for as long as 2 weeks and then recurred. The blood usually came from both nostrils, and sometimes amounted to a "large wash-basin full."

From time to time, there were "pins-and-needles" sensations in the fingertips. The tongue became sore, and there was some nausea, and generalized weakness. Because of increasing dyspnea, orthopnea and occasional precordial pain on exertion, the patient was unable to walk more than a few feet.

In 1933, she entered the hospital for the first time because of these symptoms. She remained for 2 months, during which she was given a transfusion and iron and ammonium citrate. Three small hemorrhages occurred from the nose during this admission. Because of home problems, the patient was discharged, with no complaints except fatigue.

After discharge, she continued taking iron quite regularly for about a year and thereafter intermittently. She soon began to suffer again from nosebleeds, mostly from the left side, occurring one to three times weekly. She remained fairly well, however, until 1936, when she developed symptoms similar to those complained of on the first admission — in addition to bouts of vomiting, feverishness, night sweats and some ankle edema.

Eight months later, the patient entered the hospital again. The treatment consisted of transfusions, iron and daily intramuscular injections of liver extract. The patient was discharged in 5 weeks feeling quite well.

From this time on, although the patient at each hospital entry showed marked anemia, the source of blood loss was obscure. In 3 years, during which she took iron intermittently, she had three admissions to the hospital. Her complaints were similar to those noted on the first two admissions, but except for occasional streaks of blood after blowing her nose, no history of gross epistaxis could be obtained. The only other source of blood loss was infrequent bleeding from hemorrhoids. The patient denied tarry stools. Treatment each time was essentially similar to that noted on the last admission and was always effective.

In 1917, after a "blood test," the patient was given intravenous and intramuscular medication for several years. Then, she was told that her "blood was negative." In 1918, she had "rheumatic arthritis" for a few months. She apparently required no bed rest. In 1937, she was told that she had "rheumatic heart disease." Because of her economic situation, her diet had always been rather low in meat.

The hospital records showed that her mother had severe nosebleeds, anemia and telangiectases of the lips, tongue and fingers; an autopsy report at another hospital noted "severe anemia and multiple bleeding points in the gastric mucosa." The patient stated that her grandmother, great-aunt and great-grandmother supposedly died of "bleeding diseases." She had one daughter, who had had no history of bleeding or telangiectasia.

Physical examination showed a well-developed, middle-aged woman, who was orthopneic, dyspneic and pale. On the anterior portion of the tongue, especially, there were several small, round, bright-red papules, 2 to 3 mm. in diameter (Fig. 1). In addition, telangiectases were noted on the left cheek, the mucocutaneous junction of the upper lip, the right conjunctiva, and all over the nasopharynx.

During the patient's first admission, nose and throat consultants found scales in both nares, but no bleeding. At the last entry, a few small telangiectatic spots were seen on the anterior septum and also on the lateral nasal walls. At the mucocutaneous junction of the left naris were two small telangiectatic areas. The left anterior septum showed a large superficial ulcer of the mucosa. The only actual point with crusted blood was over this ulcer. At

*Formerly, house officer, Third Medical Service (Tufts), Boston City Hospital; resident, First Medical Service (Tufts), Boston City Hospital.

most entries, there was clotted, red blood in the left nostril. The palate, the posterior pharynx and the roof of the nasopharynx also showed telangiectases. No attempt was made to treat these lesions, because none could be proved as the source of the bleeding.

The fundi were normal except at the first admission, when each fundus showed a small red area suggestive of hemorrhage.

During several admissions, the cardiac findings varied. At one time, a high-pitched, blowing systolic murmur was heard all over the precordium; the pulmonic second sound

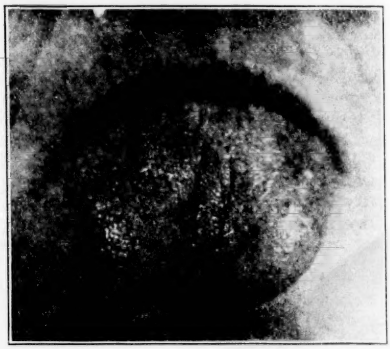

FIGURE 1. *Photograph of Tongue of Patient C. G., Showing Telangiectases.*

was greater than the aortic; the heart was slightly enlarged to the left by percussion. On another occasion, systolic and presystolic murmurs were heard at the apex. During the last admission, a Grade 2 systolic murmur was heard best in the 4th left interspace, 4 cm. to the left of the midsternal line, and a few medium moist rales were present at the right base.

At the last entry, there was a slight tenderness in the right upper quadrant, and the liver was felt three or four fingerbreadths below the costal margin. Previous to this admission, tenderness in the right upper quadrant was noted once, the liver was questionably palpable another time, and definitely felt down to the umbilicus on another occasion. The spleen was not felt. At the last two admissions, there was slight pitting edema of the feet. Rectal examination showed three or four anal tabs and small hemorrhoids. The vaginal examination was negative.

On the several admissions, the temperature varied from 98.8 to 100.2°F., the pulse from 88 to 124, and the respirations from 25 to 28.

The hemoglobin level and red-cell count at the time of each entry and discharge are presented in Table 1.

The white-cell counts varied from 7400 to 19,000. On the occasion when they were elevated, they quickly fell to normal. On the first admission, the mean corpuscular volume was 69.8 cubic microns, the mean corpuscular hemoglobin, 13.7 micromicrograms, and the mean corpuscular hemoglobin concentration, 19.5 per cent. From 3.3 to 14.5 per cent reticulocytes were found, the latter occurring as a peak count following the administration of iron. A typical smear showed 82 per cent polymorphonuclears, 1.5 per cent basophils, 1 per cent eosinophils, 6 per cent small lymphocytes, 2 per cent large lymphocytes, 7 per cent monocytes and 0.5 per cent myelocytes; there were occasional normoblasts, increased and large platelets, poikilocytosis and anisocytosis. One smear showed decreased platelets. The bleeding time was about 4 minutes; once, it was reported to be over 10 minutes. The clotting time was 5 to 8 minutes; on one occasion, it was noted that clot retraction was poor. The tourniquet test was negative, and the prothrombin time was normal. The red blood cells hemolyzed in solutions containing 0.44 to 0.36 per cent sodium chloride.

The cholesterol was 84 mg., the uric acid 4.7 mg., the nonprotein nitrogen 22 mg., the calcium 8.8 mg., and the

TABLE 1. *Hemoglobin Levels and Red-Cell Counts at Each Admission.*

ADMISSION	DATE	HEMOGLOBIN LEVEL %	RED-CELL COUNT $\times 10^6$
First	1/25/33	8	0.9
	3/24/33	30	2.3
Second	9/14/37	9	1.8
	10/21/37	75	4.4
Third	6/23/38	10	0.9
	7/23/38	64	3.1
Fourth	1/9/39	1.8 gm.	1.2
	1/26/39	6.4 gm.	2.0
Fifth	9/23/40	10	1.2
	11/5/40	56	2.8

phosphorus 3.7 mg. per 100 cc. The phosphatase was 4.3 Bodansky units, and the icteric index, 2; the blood was Type IV (Moss); the blood Hinton reaction was negative, and the formol-gel test was negative.

The urine showed a specific gravity of 1.008 to 1.011, a negative test for albumin and a few white blood cells per high-power field in the sediment. The specific gravity on each sample of urine obtained was in this range. No concentration tests were done.

No stools were studied at the first admission; on the second admission, one stool gave a +++ guaiac reaction; on the third admission, many stools gave up to ++++ guaiac reactions and were still strongly positive on discharge; at the fourth admission, one stool was benzidine negative; and on the fifth admission, many stools gave + to ++++ guaiac reactions and were strongly positive on discharge.

Typical electrocardiograms showed a sinoauricular tachycardia and rather low voltage.

Gastric analyses on four occasions showed no free hydrochloric acid, even after histamine. On the first analysis, no guaiac test was recorded. The other three were done during the last admission, and the tube was passed through the mouth on each occasion. One was guaiac negative, and the other two showed gross fresh blood.

Two barium enemas showed incomplete filling of the cecum; a third examination 6 months later was completely negative.

Three gastrointestinal series were negative. The last was done with follow-through studies because of the barium enema results first obtained.

Sigmoidoscopy showed a normal, pale mucosa.

Following final discharge, the patient was observed for 6 months. The hemoglobin level and red-cell count climbed slowly to 65 per cent and 3,500,000, respectively, although the stools showed a persistent ++ to +++ guaiac reaction.

Discussion

In most cases of hereditary telangiectasis, the hemoglobin very rarely falls to such low levels as those recorded in this case. Houser[3] states that the mortality from hemorrhage is 4 per cent. In most of the cases in the literature, the hemoglobin was noted to be from 50 to 60 per cent.

The patient's diet, which had not been completely adequate, could not explain the picture of anemia without obvious bleeding. During the first two admissions, the source of the blood loss was obvious. In subsequent admissions, the nose could not be incriminated, except for the possibility of postnasal drip, of which the patient was unaware. This was never observed during the last admission, even though she was examined before arising from the horizontal position in the morning.

The only obvious bleeding point in the later hospital entries was a superficial ulcer on the septum. This showed clotted blood on several admissions. The aural consultants did not consider this lesion sufficient to cause the marked anemia. O'Kane[4] reported a case with a ++++ guaiac reaction in the stool that cleared only on treatment of the nasal telangiectases with a sclerosing solution. In his case, the hemoglobin was 50 per cent, and the red-cell count was 3,100,000.

This patient presented the problem of a possible primary lesion in the gastrointestinal tract, as suggested by the first barium enemas. She had a large liver on several entries; this was noted definitely for the first time, three years before the last entry. During the last admission, the liver did not shrink more than 1 cm. as the cardiac failure was relieved. No nodularity of the liver was observed. A final gastrointestinal series and another barium enema six months later did not reveal a cecal lesion. The patient's good and repeated response to treatment and the failure to lose weight also militate against the view that a primary cecal lesion might have been responsible for the melena.

Boston[5] and Goldstein[1] presented cases of gastric hemorrhages due to telangiectases. In the case reported above, two gastric analyses during the last admission showed fresh blood, although the samples were removed through the mouth; however, a properly handled Levin tube does not usually give fresh blood. The mother's autopsy showed "bleeding points" in the gastric mucosa. Gastrointestinal telangiectases must be strongly considered in both the patient and her mother.

Fitz-Hugh[6] has drawn attention to a marked intolerance to blood transfusion, resulting in severe jaundice, in patients with Type IV blood and splenomegaly and hepatomegaly. This patient was Type IV and presented hepatomegaly, but no splenomegaly. She had eight transfusions. Three moderate chills, one with vomiting, were the only reactions recorded.

One final interesting fact has been noted by several observers — namely, the disappearance of some lesions and the appearance of others. Apparent fundic lesions described in the first admissions have since disappeared.

Summary

A case of hereditary telangiectasis that fulfilled the criteria for diagnosis is presented. The patient showed a very marked anemia on repeated occasions, at first because of nasal hemorrhage, later possibly as a result of gastrointestinal bleeding. The possibility of a separate pathologic lesion in these cases must be kept in mind, but this seems to be ruled out in the case under discussion.

References

1. Goldstein, H. I. I. Goldstein's heredofamilial angiomatosis with recurring familial hemorrhages (Rendu-Osler-Weber's disease). *Arch. Int. Med.* **48**:836-865, 1931. Hereditary multiple telangiectasia. *Arch. Dermat. & Syph.* **26**:282-308, 1932.
2. Larrabee, R. C., and Littman, D. Hereditary hemorrhagic telangiectasia: with a report of five cases in two families. *New Eng. J. Med.* **207**:1177-1182, 1932.
3. Houser, K. M. Hereditary hemorrhagic telangiectasia. *Ann. Otol., Rhin. & Laryng.* **43**:731-738, 1934.
4. O'Kane, G. H. Hereditary multiple telangiectasis with epistaxis. *J. A. M. A.* **111**:242-244, 1938.
5. Boston, L. N. Gastric hemorrhage due to familial telangiectasis. *Am. J. M. Sc.* **180**:798-802, 1930.
6. Fitz-Hugh, T., Jr. Splenomegaly and hepatic enlargement in hereditary hemorrhagic telangiectasia. *Am. J. M. Sc.* **181**:261-268, 1931.

MEDICAL PROGRESS

HEMATOLOGY: ANEMIA, WITH PARTICULAR REFERENCE TO THE HEMOLYTIC SYNDROME*

WILLIAM DAMESHEK, M.D.†

BOSTON

ANEMIA is but a symptom and is therefore always secondary to some other disorder, and so-called "primary" anemia is a thing of the past. Modern classifications of anemia stress cell size and the color index. Thus, anemias are either macrocytic, normocytic and microcytic or hyperchromic, normochromic and hypochromic. These classifications are very useful, since macrocytic, hyperchromic anemias are often deficient in "liver-extract" or vitamin B complex; normocytic, normochromic anemias often indicate that the bone marrow itself is involved by hypoplasia, aplasia, sclerosis, leukemia or metastatic cancer, whereas microcytic hypochromic anemias usually mean that red-cell formation is normal but that hemoglobin is either lacking (iron-deficiency anemia) or cannot be properly synthesized.

HYPOCHROMIC MICROCYTIC ANEMIAS

A deficiency in iron for the available red-cell formation in both the bone marrow and the blood results either from continued blood loss or from such abnormalities as an inadequate intake of iron in the food, achlorhydria, malabsorption from the bowel and multiple pregnancies. Usually, multiple etiologic factors are necessary before a well-defined anemia results. The condition often known as idiopathic or primary hypochromic anemia, which is usually described in middle-aged women, is also the end result of numerous factors, the most important of which is perhaps the complete histamine achlorhydria. That this condition may be a forerunner of pernicious anemia has been stated a number of times. Miller and Dameshek[1] report 2 cases of primary hypochromic anemia that terminated as pernicious anemia. The first case showed "sideropenic dysphagia," generally known as the Plummer–Vinson syndrome, and developed pernicious anemia a number of years after a typical hemoglobin deficiency had been found. The second case appeared to be a typical case of chronic iron deficiency until iron was given, following which the features of pernicious anemia became apparent. These cases are of some theoretical interest, since they indicate that the gastric mucosa may first be incompletely atrophic, leading to a disturbance in the digestion of iron-containing foods, and later completely atrophic, resulting in such great diminution in the secretion of Castle's enzyme that the liver-extract deficiency state known as pernicious anemia results. It is probable, as Miller and Dameshek pointed out, that the gastric disturbance starts early in life and, if sufficiently marked in adolescence and early adulthood, may result in the development of the iron-deficiency anemia known as "chlorosis." This condition is by no means extinct, as both A'sted[2] and Olef[3] have shown. Although Olef attempts a clear-cut discrimination between chlorosis and the so-called "primary hypochromic anemia," such a differentiation is probably to be questioned, since the cases merge into one another and, except for age, are really identical in underlying physiology, objective signs and response to therapy. Chlorosis is in all probability idiopathic hypochromic anemia in a somewhat younger age group than most of the cases. When the latter are analyzed, however, a history of long-standing anemia extending back fifteen to thirty years is usually obtained. This illustrates again the value of analyzing the life history of a disease rather than of interpreting it from a single snapshot.

Work on the absorption and metabolism of iron by means of radioactive iron continues in several laboratories.[4] Ross and Chapin[5] found that the greatest absorption took place in patients with chronic hypochromic (presumably, iron-deficiency) anemia. By this method, cases of pernicious anemia were found to have an iron deficiency that became apparent only after the erythrocyte response to liver extract had occurred. Fowler and Barer,[6] who studied this problem without recourse to the radioactive technic, suggested that iron had, in addition to its action as replacement therapy, a stimulating effect on hemoglobin formation. In another investigation, the same authors[7] discovered that the addition of copper sulfate to the iron preparation (ferric ammonium citrate) used did not

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, 1940* (Springfield, Illinois: Charles C Thomas Company, 1941. $4.00).

*From the Joseph H. Pratt Diagnostic Hospital, and the Blood Clinic of the Boston Dispensary.

†Visiting physician and consulting hematologist, Joseph H. Pratt Diagnostic Hospital; chief, Blood Clinic, Boston Dispensary.

increase the effectiveness of iron in the hemoglobin regeneration of mild hypochromic anemia in the adult.

Hyperchromic Macrocytic Anemias

Pernicious Anemia

Despite minor modifications, Castle's theory regarding the interaction of intrinsic factor derived from the stomach and extrinsic factor derived from the food continues to stand firm. Very careful and elaborate observations by Formijne[8] demonstrated again that liver extract was not formed by the interaction of extrinsic and intrinsic factor in vitro, and could be produced only in vivo. A series of carefully controlled observations in swine — in which total gastrectomy was performed, the animals killed at various intervals, and the livers assayed for potency by testing in human cases of pernicious anemia — is reported by Geiger, Goodman and Claiborn.[9] Following total gastrectomy, the liver gradually became depleted of antianemic potency; this indicates that it serves either as a storage reservoir or as an elaborating and storing center. By other ingenious experiments, it was confirmed that gastric digestion was essential for the production of the erythrocyte-maturation factor, although it was also shown (as Meulengracht had previously indicated) that the duodenum is a significant source of intrinsic factor. Despite removal of the entire stomach and the duodenum, with great reduction in the antianemic potency of the swine's liver, it was, however, impossible to produce in these animals the typical human blood picture of pernicious anemia. Ivy[10] and Wintrobe and his co-workers[11] have also failed to produce the blood picture of pernicious anemia either by gastrectomy in various animals or by the use of a diet grossly deficient in various factors of the vitamin B complex. Wintrobe et al. were, however, able to produce neurologic phenomena closely resembling those found in pernicious anemia by a diet deficient in pantothenic acid, pyridoxin and choline. Whether these studies have any definite relation to pernicious anemia remains to be seen.

The long-standing question regarding the relation of the fish tapeworm (*Diphyllobothrium latum*) and pernicious anemia is still under discussion. Von Bonsdorff[12] reports 14 typical cases of pernicious anemia in carriers of the worm. In the first 9 cases, treatment with an anthelmintic filicin was followed by a distinct reticulocyte response and a complete remission; liver extract was not used. Reticulocytosis began directly after expulsion of the worm. In 1 case, liver extract was necessary for a complete remission. In the last 4 cases, the worm cure had little or no effect on the anemia, which was completely relieved by liver extract. In these cases, there was apparently only a coincidental relation between the simultaneous presence of the worm and the severe anemia. Von Bonsdorff believes that in many cases the tapeworm interferes with the absorption of the liver-extract substance from the bowel, and that although the anemia can be cured with liver extract, removal of the worm is of fundamental importance.

Jones[13] and Meyer, Schwartz and Weissman[14] discuss the problem of gastrectomy and the anemias. Jones states, "It is apparent that major gastric surgery may be performed without any great fear of undue consequences as far as the factor of normal hematopoiesis is concerned . . . [although] an occasional severe microcytic or macrocytic anemia may ensue . . . many months following operation." Meyer and his co-workers report such a case, which five years after complete gastrectomy developed pernicious anemia. The value of long-continued observation of patients who have undergone extensive gastric operations is stressed.

Although pernicious anemia in the Negro is usually considered extremely rare, McCracken[15] reports 3 cases and states that the incidence of the disease in the Negro is 1 per 100,000, as compared with 35 per 100,000 in the white race. Schwartz,[16] who has observed a large number of cases of pernicious anemia in Negroes at the Cook County Hospital, Chicago, stresses the diagnostic difficulties in some of the cases, which may masquerade as a subacute or chronic infectious process.

Treatment of the disease has been quite well standardized in this country, since the various products have been assayed and labeled according to their unit potency. Such assays must still be performed in previously untreated human cases, because no satisfactory animal method has been found. Worth watching, however, is the method of Crandall, Finne, and Smith,[17] which utilizes dogs with internal bile fistulas (anastomosis of the gall bladder to the right renal pelvis, with ligation of the common bile duct). A hyperchromic, macrocytic anemia, apparently responding to liver extract, gradually follows this operation. Jacobson and Subbarow[18] report on recent advances in the purification of active substances from liver extract. Although the primary factor has still not been obtained in crystalline form and several factors are probably required to give the full effect, these investigators report that recent refinements in preparation have resulted in the development of a material that is highly effective in an average dosage of only 7 mg. every ten days.

Askey,[19] arguing that the liver in a case of pernicious anemia is completely lacking in specific

substance, suggests the use of a single massive dose of liver extract (150 to 400 *U.S.P.* units) given intramuscularly without other treatment. Clinical and hematologic responses were excellent and well maintained in the majority of the cases for several months. A massive initial dose to "stock the liver," followed by monthly doses to maintain adequate storage, appeared sufficient to give optimum results in most cases. This method of therapy cannot be recommended. It is not known how much of the massive dose is quickly excreted in the urine; stocking the liver is not the essential thing; curing the liver-extract deficiency throughout the body is essential, and the most physiologic method possible should be used. For this reason, regular doses — preferably every week or two — are far preferable, although still not entirely physiologic. Evans and Jordan[20] found that a highly concentrated liver-extract preparation in 1-cc. doses parenterally was more effective both hematologically and neurologically than the cruder preparations. Neural symptoms and signs were controlled or actually improved in the great majority of cases. Zillhardt, MacLean and Murphy[21] found that the combination of thiamin (vitamin B_1) and parenteral liver extract "might have a beneficial effect on those residual neural signs and symptoms of pernicious anemia that seemed stationary in spite of persistent, intensive antipernicious anemia therapy." The authors rightly advise caution in the interpretation of their results. No effects were obtained when the vitamin was given orally, or when vitamin B complex (containing thiamin) was given parenterally.

Hemolytic Syndromes

Interest in the numerous hemolytic syndromes continues to run unusually high. They may be classified as follows:

A. Hemoglobinurias (exceedingly rapid hemolysis, with hemoglobinemia and hemoglobinuria)
   1. Paroxysmal cold
   2. Paroxysmal nocturnal
   3. March
   4. Favism
   5. Unclassified types

B. Hemolytic anemias
   1. Hereditary
      a. Spherocytic
      b. Target-cell (Mediterranean)
      c. Sickle-cell (African)
   2. Acquired (acute, subacute and chronic types)
      a. Chemical, including the sulfonamide drugs
      b. Immune body (hemolysins and agglutinins), including erythroblastosis foetalis
      c. Idiopathic, including hypersplenic types
      d. Symptomatic

Although this classification seems to offer some help, it is realized that it probably has only transitory significance. It is somewhat unorthodox in that hereditary (usually called "congenital") hemolytic jaundice or anemia, which is generally considered to be spherocytic, is subdivided into spherocytic, target-cell and sickle-cell types; it will be noted, furthermore, that erythroblastosis foetalis is included under the acquired hemolytic processes in association with the presence of immune bodies.

Mechanisms

Much discussion continues to center about the etiologic mechanisms relating to the hemolytic syndromes. In some, as in paroxysmal cold hemoglobinuria, these have been rather well worked out; in others, they are as obscure as ever. It should be realized that increased blood destruction may be due to numerous causes and that multiple mechanisms are often present. A theory that attempts to explain all the hemolytic syndromes on the basis of a single mechanism must on occasion be stretched rather fine. Theories at present being discussed are as follows:

Hereditary defect of "erythron." This is accepted by most authors as the cause for congenital spherocytic hemolytic jaundice, and perhaps also for the target-cell and sickle-cell types. Unless they are caused by some definite etiologic agent, many acquired cases with spherocytosis are even said by extreme protagonists of this view to be due to a congenital defect of the red cells, latent for many years.

Stasis. The chief protagonists of this theory are Ham and Castle,[22] who point out that stasis results in increased spheroidicity of the red cell and, ultimately, in its hemolysis. Hemolytic reactions are thought to be due to extreme stasis, especially in the spleen, or to agglutinative reactions. This theory does not explain, among other conditions, march hemoglobinuria or the hemolytic syndromes associated with actual hemolysins.

Hemolysins. Dameshek and Schwartz[23] found hemolysins in the blood in certain cases of acute hemolytic anemia, and by the injection of immune hemolysins they were able to reproduce spherocytosis and various types of hemolytic syndromes.[24] They contended that hemolysins might be at the bottom of many of the hemolytic syndromes, including congenital spherocytosis. If by "hemolysin" is meant an agent — chemical, immune-body or cellular — that causes injury to red cells, this idea may be well taken, although the hemolysis of simple stasis, unusual exertion and so forth is not explained. Although Ham and Castle prefer to designate the hemolysis following agglutination

as a phenomenon of stasis, Dameshek and Miller[25] have shown that agglutination causes injury to the red-cell envelope, with the result that it becomes readily vulnerable to mechanical trauma, stasis and the effects of complement activity.

Lysolecithin. Bergenhem and Fahraeus[26] demonstrated that normal blood serum contains a lytic substance, which they called "lysolecithin." They demonstrated that it became increased with stasis and concluded that it was responsible for normal blood destruction in the chief organ of stasis — the spleen. They suggested that hemolytic anemias might simply be due to an increased concentration of lysolecithin acting on the erythrocytes passing slowly through the spleen. Singer[27] described a method for the extraction of lysolecithin from the serum and for quantitative measurement of its hemolytic power. He also described the lysolecithin fragility test, apparently specific for the spherocytes of congenital hemolytic jaundice. In a later paper, Singer[28] pointed out that "the significance of lysolecithin as the physiological hemolysin involved in the mechanism of normal blood destruction . . . is not conclusive," and that it was not likely that lysolecithin could be regarded as responsible for the increased blood destruction in congenital hemolytic jaundice, especially since no increase in the production of this lysin was demonstrable in the disease. Singer concluded that lysolecithin, although it had hemolytic qualities, was not the hemolysin causing hemolytic anemia.

Spleen. Because of the dramatic effects of splenectomy in many cases of hemolytic anemia, of both the congenital and acquired types, the spleen has naturally been singled out as the chief offender by most observers. What the spleen actually does still remains a mystery. According to Ham and Castle,[22] it acts like a test tube, allowing normal red cells to stagnate and become somewhat spheroidal and causing the abnormal spherocyte to become hemolyzed. According to Bergenhem and Fahraeus,[26] lysolecithin and the spleen are closely related. Dameshek and his co-workers[24, 29] assume that the spleen is the chief organ of hemolysin production, and other observers, notably Doan,[30] arrive at a somewhat similar conclusion by stating that blood destruction has to do with the reticuloendothelial system, of which the spleen is the largest factor. That some cases of hemolytic anemias are solely hypersplenic cannot be denied; in others, the spleen seems to be secondarily enlarged, and splenectomy may or may not be of value. Direct observation of the living spleen in the rat by means of transilluminated quartz rod was first performed by Knisely,[31] and on the basis of his work, it seemed clear that circulation in the spleen is of the closed variety and that blood often stagnates there, perhaps for hours. However, in a more recent communication, MacKenzie, Whipple and Wintersteiner,[32] using a modification of the same technic, came to diametrically different conclusions — that is, that the spleen possessed an open circulation and that the pulp spaces, not the venous sinuses, were the primary physiologic units of the splenic vascular mechanism. Studies of the spleen in experimentally produced hemolytic anemia revealed that spherocytes were trapped outside sinusoids and then presumably became hemolyzed. Singer, Miller and Dameshek[29] studied subjects splenectomized for various causes and found that blood destruction, as measured by the fecal urobilinogen output, became greatly reduced; this might be associated with the fact that a thinner, more resistant cell population, together with increased numbers of target cells, was present. The spleen was found to have other functions, which are described below. From all these studies, it may safely be concluded that the exact relation of the spleen to hemolytic anemia is not yet clear, nor can one say with any degree of assurance which of the various theories described above fits most closely the pattern of the observed facts.

Hemoglobinurias

Paroxysmal nocturnal hemoglobinuria. This disorder, which has been studied extensively by Ham[33] and by Ham and Dingle,[34] is associated with an increase in the acid fragility of the red cells. The fundamental cause of the disorder remains obscure, although there is some evidence that the red cells are injured by an immune body (hemolysin?) since complement results in hemolysis. Ham and Horack[35] made the interesting observation that certain cases of chronic hemolytic anemia may not show the characteristic nocturnal episodes of hemoglobinuria except at infrequent intervals. The acid fragility test of Ham thus becomes an important diagnostic test in atypical hemolytic syndromes, especially when splenectomy is being considered, since removal of the spleen is without therapeutic effect in paroxysmal nocturnal hemoglobinuria.

March hemoglobinuria. Gilligan and her collaborators[36, 37] have made careful studies of the interesting condition known as march hemoglobinuria. In this curious condition, first described in soldiers, "black water" develops with specific types of exercise, such as strenuous marching and running. Hemoglobinuria does not develop when the patient assumes a kyphotic instead of a lordotic position while exercising. Gilligan et al. studied the

renal threshold for hemoglobin in the blood plasma, its quantitative excretion in the urine, the spectrophotometric analysis of the pigment and various possible pathogenetic mechanisms. No clues regarding the etiology of the condition were found, although much useful information concerning the pathologic physiology of the hemoglobinurias was obtained.

Favism. Luisada[38] has contributed a comprehensive article on favism, which he considers "a singular disease chiefly affecting the red blood cells." This condition, which is chiefly restricted to the inhabitants of Sardinia, results either from the ingestion of the fava bean or from inhalation of its flowers, and is characterized by the sudden appearance of hemoglobinuria, jaundice and vascular symptoms. Luisada believes that the condition represents an anaphylactic reaction in which the red cells are directly injured.

Other hemoglobinurias. Altschule and Gilligan[39] report a case of acute, massive hemoglobinuria in an old man without demonstrable cause and bearing, apparently, little relation to the other types of hemoglobinuria. This study is distinguished chiefly by the careful measurements of the various metabolic changes in blood pigment, and by the discussion of the differential diagnosis of hemoglobinuria. Calculations of the amount of hemoglobin lost during the attack, as computed by various methods, showed that approximately 1400 cc. of blood was hemolyzed during the first week, 400 cc. during the second week, and 200 cc. during the third. In another paper, Gilligan and Kapnick[40] reported hemoglobinuria occurring during treatment with sulfanilamide. It is recommended that, in addition to transfusions, sodium bicarbonate be added in sufficient quantity to keep the urine alkaline. This is said to protect the kidneys against damage caused by deposition of hemoglobin pigment in the tubules.

Hereditary Hemolytic Anemias

Spherocytosis. Lloyd[41] has contributed a significant (unfortunately not very accessible) monograph on the etiology of "acholuric family jaundice," in which the various abnormalities in the disease are assessed according to the theories discussed above. Singer's[28] finding that the spherocytes of this disease are abnormally fragile to lysolecithin is confirmed, and Lloyd also agrees with Singer that there is not enough evidence to incriminate lysolecithin. Some very ingenious experiments are recorded in which exsanguination was performed on a newborn monster and transfusions were given (on separate occasions) from 2 persons with congenital hemolytic spherocytic jaundice, one of whom had been splenectomized, the other being an active case. The recipient lived long enough for observations to be made. Whereas the red cells of the splenectomized patient became rapidly more spherocytic and were quickly destroyed in the circulation of the monster (who possessed a normal spleen), the red cells of the active spherocytic case became no more spherocytic than in their own circulation. From these observations, the author concludes:

> The pathological blood destruction of the disease is dependent upon the inheritance of an abnormality of the erythron. As the result of this defect the red cells are abnormally susceptible to damage in their passage through the spleen by a process which, very probably, causes little or no permanent damage to the normal erythrocyte. . . . It is possible that lysolecithin . . . will cause permanent damage to the red cells of acholuric family jaundice, indicated by spherocytosis which persists until the death of the cell, but which is not sufficient to cause permanent alteration in the normal erythrocyte.

These in vivo experiments result in conclusions similar to the in vitro findings of Ham and Castle,[22] but they still do not explain the "why" of the congenital spherocytosis, which may be the result of the activity of an inherited hemolytic factor on the non-nucleated erythrocyte. Nor is the abnormally diminished blood destruction following splenectomy in this congenital type of hemolytic jaundice explained[33] — that is, although spherocytosis is still present, blood destruction is less than normal, indicating that the spherocyte has a normal resistance within the circulation and that the spleen has an active (hemolytic?) effect in destroying erythrocytes. This is also indirectly brought out in the report of a series of 3 cases of hemolytic crisis occurring in 3 members of one family with hereditary spherocytic jaundice.[42] That all these persons developed very severe anemia, necessitating emergency splenectomy within a few days of each other, makes it possible that the cause of the suddenly enhanced spherocytosis was outside the marrow and perhaps splenic in origin.

Dameshek and Singer[43] direct attention to a type of familial jaundice without bile in the urine and nonhemolytic in type (familial nonhemolytic jaundice). This condition, in which persistent although somewhat variable and usually mild jaundice is present, may be confused either with familial hemolytic jaundice or with mild hepatic disease. It is distinguished from the former by the normal size, thickness and fragility of the red cells, by the lack of reticulocytosis and by the absence of all evidence of increased blood breakdown, particularly in the fecal urobilinogen out-

put. It is distinguished from hepatic disease by the long course, its familial nature and the complete normality of the liver-function tests. As demonstrated by the bilirubin-excretion test, the condition is apparently due to a delayed excretion of indirect bilirubin from the blood stream by the liver cells, with resultant retention. The liver itself is histologically normal, as recently shown by Krarup and Roholm.[44] A very careful evaluation of the bilirubin-excretion test is that of Weech, Vann and Grillo.[45]

Target-cell anemia. Under this designation, I[46] described the case of an Italian youth who showed marked hypochromic anemia, jaundice, marked splenomegaly, generalized osteoporotic changes and the presence of many target cells in the blood. These cells, which look like a target or bull's eye in stained preparations, are abnormally thin and unusually resistant to hypotonic saline solutions. Because this patient presented most of the features of Cooley's anemia, and because cases of this Mediterranean disease show not only nucleated red cells but target cells and increased hypotonic resistance in the blood, the possibility was broached that the fundamental defect in both conditions was the target cell. Wintrobe, Matthews, Pollack and Dobyns,[47] reporting a similar condition in 14 members of three Italian families, stated that both Cooley's anemia and this milder Mediterranean condition represented an inherited defect — the production of unusually thin red cells. Other reports of what is probably the same condition are those of Strauss, Daland and Fox[48] and of Eliel and Bayles.[49] From further studies of these conditions,[50] it appears that familial target and oval syndromes are relatively common in Italian families, that they are inherited as a dominant characteristic, and that great variabilities occur in their severity. Thus, Cooley's anemia appears to be the severest form, and target-cell anemia the next, a number of milder forms ("hypochromic polycythemia," refractory hypochromic anemia and so forth) being known.

Bohrod[51] rightly points out that the target cell is commonly found in many, particularly hypochromic, anemias. Barrett[52] first noted that these cells were found in unusually large numbers in sickle-cell anemia, following splenectomy and in obstructive jaundice and steatorrhea. Singer, Miller and Dameshek[29] found them constantly in splenectomized patients and explained the increased hypotonic resistance of the red blood cells on this basis. Bohrod attacks the concept that the target cell represents a cell that is perhaps defective, and maintains that it is merely representative of increased blood regeneration secondary to blood destruction or blood loss. This view does not agree with the observations that, following splenectomy, blood destruction is conspicuously diminished and target cells become greatly increased, that, in the familial Mediterranean cases, target cells are frequently numerous without any evidence of increased blood destruction, that, following splenectomy in Cooley's anemia, large numbers of target cells appear or that these cells are absent from cases of congenital and acquired spherocytic jaundice in which blood destruction is greatly increased.

Sickle-cell anemia. Bauer[53] contributes a comprehensive article on sickle-cell disease, in which valuable considerations regarding pathogenesis and the generalized character of the condition are discussed. Anemia is only one consequence of the sickle-cell trait, and is much less serious than the circulatory stasis in the small blood vessels of the internal organs, which is perhaps the primary and most disastrous consequence of the disease. Such stasis may be enhanced by surgical procedures and may be the fundamental cause of the anemia. It is recommended that all Negro patients be routinely examined for the sickle-cell trait, since this condition may result in disorders mimicking rheumatic fever, rheumatic heart disease, polyarthritis, osteomyelitis, various infectious diseases, cerebral conditions, peptic ulcer, appendicitis and so forth. Sickle-cell anemia with unusual bone changes is reported by Danford, Marr and Elsey,[54] with central-nervous-system involvement by Hughes, Diggs and Gillespie[55] and by Skoog,[56] and with ulcers of the legs by Cummer and LaRocco.[57] The reason for the development of these ulcers is still obscure despite very careful studies. Methods for the determination of the sickle-cell trait are described by Diggs and Pettit[58] and by Sherman.[59] The moist stasis method — Scriver and Waugh[60] — is recommended by Diggs and Pettit. Sherman describes a method for differentiating the sickle-cell trait and sickle-cell anemia by injecting red cells kept free from outside air into a solution of saline formalin. Since the sickle-cell trait may have no clinical significance, it is essential to differentiate it and the actual sickle-cell anemia.

Acquired Hemolytic Anemias

Fox and Ottenberg[61] present a careful study of the acute hemolytic anemia resulting from the sulfonamide drugs. This may be so severe as to result in shock and even death; in fact, 6 of their 9 cases ended fatally. The fundamental mechanism of the blood destruction is still obscure, although it may be allergic or due to the formation of unusual oxidation products that are

FRANKLIN SQUARE HOSPITAL LIBRARY

allergic or hemolytic. Emerson, Ham and Castle[62] came to similar conclusions. Fox and Ottenberg found that twelve to forty-eight hours after onset of hemolysis, the serum contained three blood pigments: hemoglobin, methemoglobin and Fairley's new pigment — methemalbumin.

Farrar, Burnett and Steigman[63] report a case of acquired hemolytic anemia in which a serum isohemolysin was found, similar to that found in the cases of Dameshek and Schwartz.[23] Splenectomy was curative.

Recent experience with cases of acute and subacute acquired hemolytic anemia of idiopathic variety reveals that only occasionally are hemolysins demonstrable. Splenectomy, although usually curative, may not result in recovery, particularly if the operation has been postponed too long while numerous transfusions have been given. Under these circumstances, not only may new agglutinins or hemolysins be built up, but unusual myeloid metaplasia may develop in spleen or liver. Cases of this sort may then not respond to splenectomy. In such cases, one should determine whether greatly increased blood destruction is present and should be sure that no underlying cause, such as leukemia or Hodgkin's disease, is present; only a minimum number of transfusions (one to three) should be given before splenectomy is performed. Many cases in infants and young children are probably of a milder form (so-called "Lederer's anemia"), and these patients frequently, but by no means always, recover without splenectomy. Such a case is reported by Sterner.[64]

Levine, Katzin and Burnham[65] indicate that erythroblastosis foetalis — icterus gravis neonatorum — is acute hemolytic anemia of the newborn and is caused by isoimmunization of an Rh– mother by an Rh+ fetus. The resultant anti-Rh agglutinin may then penetrate the placental circulation and cause agglutination, with consequent hemolysis of the infant's red cells. It is extremely important in these cases to give blood from an Rh– donor — *not* the mother. If testing for the Rh factor cannot be done, extremely careful crossmatching by means of the Landsteiner test-tube technic should be performed, with the modification that incubation of the serum, red-cell suspension and saline mixture be carried out for at least thirty minutes. By proper transfusion technic in these cases, the mortality rate should be considerably reduced.

The possibility that some cases of acquired hemolytic jaundice are secondary to some underlying process such as leukemia, Hodgkin's disease, lymphosarcoma or dermoid cyst is suggested by Singer and Dameshek.[66] In one remarkable case in which splenectomy resulted in only a temporary response, the finding and removal of a dermoid cyst resulted in complete cure.

113 Bay State Road

References

1. Miller, E. B., and Dameshek, W. "Primary" hypochromic anemia terminating in pernicious anemia: report of two cases. *Arch. Int. Med.* **68**:375-394, 1941.
2. Alsted, G. Chlorosis. Essential juvenile iron deficiency anemia. *Am. J. M. Sc.* **201**:1-11, 1941.
3. Olef, I. Chlorosis. *New Eng. J. Med.* **225**:358-365, 1941.
4. Dameshek, W. Hematology. *New Eng. J. Med.* **224**:729-741, 1941.
5. Ross, J. F., and Chapin, M. A. The selective absorption of radioactive iron by normal and iron-deficient human subjects. *J. Clin. Investigation* **20**:437, 1941.
6. Fowler, W. M., and Barer, A. P. Some effects of iron on hemoglobin formation. *Am. J. M. Sc.* **201**:642-651, 1941.
7. *Idem.* Effect of copper and iron on hemoglobin regeneration. *J. Lab. & Clin. Med.* **26**:832-836, 1941.
8. Formiüne, P. Experiments on properties of extrinsic factor and on reaction of Castle. *Arch. Int. Med.* **66**:1191-1214, 1940.
9. Geiger, A. J., Goodman, L. S., and Claiborn, L. N. Effects of gastrointestinal resections in swine on anti-anemia potency of liver, with observations on nature and sources of materials effective in pernicious anemia. *Yale J. Biol. & Med.* **13**:259-278, 1940.
10. Ivy, A. C. Effects of gastrectomy in animals. *Am. J. Digest. Dis.* **7**:500-502, 1940.
11. Wintrobe, M. M., Miller, J. L., Jr., and Lisco, H. Relation of diet to occurrence of ataxia and degeneration in nervous system of pigs. *Bull. Johns Hopkins Hosp.* **67**:377-405, 1940.
12. von Bonsdorff, B. On reticulocyte response and course of remission after removal of worm in patients with Diphyllobothrium latum and pernicious anemia. Diphyllobothrium latum and pernicious anemia. IV. *Acta med. Scandinav.* **105**:516-539, 1940.
13. Jones, C. M. Problem of gastrectomy and the anemias. *Am. J. Digest. Dis.* **7**:502-505, 1940.
14. Meyer, K. A., Schwartz, S. O., and Weissman, L. H. Pernicious anemia following total gastrectomy. *Arch. Surg.* **42**:18-24, 1941.
15. McCracken, J. P. Pernicious anemia in the Negro. *J. M. A. Georgia* **30**:49-54, 1941.
16. Schwartz, S. O. Personal communication.
17. Crandall, L. A., Jr., Finne, C. O., Jr., and Smith, P. W. Experimental anti-pernicious anemia factor deficiency in dogs. *Science* **93**:549, 1941.
18. Jacobson, B. M., and Subbarow, Y. Studies of principle in liver effective in pernicious anemia: recent advances in purification of active substances. *J. A. M. A.* **116**:367-374, 1941.
19. Askey, J. M. Quantitative treatment of pernicious anemia: response to initial massive dose of liver extract in relapse. *J. A. M. A.* **117**:907-910, 1941.
20. Evans, T. S., and Jordan, R. H. Concentrated liver extract in maintenance treatment of pernicious anemia. *Am. J. M. Sc.* **202**:408-416, 1941.
21. Zillhardt, J. C., MacLean, K., and Murphy, W. P. Effect of thiamin on residual neural disturbances of treated pernicious anemia. *Ann. Int. Med.* **15**:33-43, 1941.
22. Ham, T. H., and Castle, W. B. Studies on destruction of red blood cells. Relation of increased hypotonic fragility and of erythrostasis to the mechanism of hemolysis in certain anemias. *Proc. Am. Philosoph. Soc.* **82**:411-419, 1940.
23. Dameshek, W., and Schwartz, S. O. The presence of hemolysins in acute hemolytic anemia. *New Eng. J. Med.* **218**:75-80, 1938.
24. *Idem.* Hemolysins as the cause of clinical and experimental hemolytic anemias: with particular reference to the nature of spherocytosis and increased fragility. *Am. J. M. Sc.* **196**:769-792, 1938.
25. Dameshek, W., and Miller, E. B. Unpublished data.
26. Bergenhem, B., and Fahraeus, R. Über spontane Hämolysinbildung im Blut, unter besonderer Berücksichtigung der Physiologie der Milz. *Zischr. f. d. ges. exper. Med.* **97**:555-587, 1936.
27. Singer, K. Lysolecithin fragility test. *Am. J. M. Sc.* **199**:466-477, 1940.
28. *Idem.* Lysolecithin and hemolytic anemia. Significance of lysolecithin production in differentiation of circulating and stagnant blood. *J. Clin. Investigation* **20**:153-160, 1941.
29. Singer, K., Miller, E. B., and Dameshek, W. Hematologic changes following splenectomy in man, with particular reference to target cells, hemolytic index and lysolecithin. *Am. J. M. Sc.* **202**:171-187, 1941.
30. Doan, C. A. The reticulo-endothelial system. In *A Symposium on the Blood and Blood Forming Organs.* 264 pp. Madison: University of Wisconsin Press, 1940. Pp. 167-193.
31. Knisely, M. H. Spleen studies. I. Microscopic observations of circulatory system of living unstimulated mammalian spleens. *Anat. Rec.* **65**:23-50, 1936. Spleen studies. II. Microscopic observations of circulatory system of living traumatized spleens, and of dying spleens. *Ibid.* **65**:131-148, 1936.
32. MacKenzie, D. W., Jr., Whipple, A. O., and Wintersteiner, M. P. Direct observations on circulation of blood in transilluminated mammalian spleens. *Proc. Soc. Exper. Biol. & Med.* **44**:139-142, 1940.
33. Ham, T. H. Studies on destruction of red blood cells. I. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria: investigation of mechanism of hemolysis with observations on five cases. *Arch. Int. Med.* **64**:1271-1305, 1939.

34. Ham, T. H., and Dingle, J. H. Studies on destruction of red blood cells. II. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria: certain immunological aspects of hemolytic mechanism with special reference to serum complement. *J. Clin. Investigation* **18:**657-672, 1939.
35. Ham, G. C., and Horack, H. M. Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinemia: report of case with only occasional hemoglobinuria and with complete autopsy. *Arch. Int. Med.* **67:**735-745, 1941.
36. Gilligan, D. R., Altschule, M. D., and Katersky, E. M. Studies of hemoglobinemia and hemoglobinuria produced in man by intravenous injection of hemoglobin solutions. *J. Clin. Investigation* **21:**177-187, 1941.
37. Gilligan, D. R., and Blumgart, H. L. March hemoglobinuria: studies of the clinical characteristics, blood metabolism and mechanism: with observations on three new cases, and review of literature. *Medicine* **20:**341-393, 1941.
38. Luisada, A. Favism: singular disease chiefly affecting red blood cells. *Medicine* **20:**229-250, 1941.
39. Altschule, M. D., and Gilligan, D. R. Acute, massive hemoglobinuria of obscure cause, with jaundice and anemia. *Arch. Int. Med.* **68:**957-978, 1941.
40. Gilligan, D. R., and Kapnick, I. Clinical and laboratory observations on hemoglobinuria occurring during sulfanilamide therapy. *New Eng. J. Med.* **224:**801-804, 1941.
41. Lloyd, T. W. *On the Aetiology of Acholuric Family Jaundice.* Oxford University Thesis, 1941. Privately printed.
42. Dameshek, W. Familial hemolytic crisis: report of three cases occurring within ten days. *New Eng. J. Med.* **224:**52-56, 1941.
43. Dameshek, W., and Singer, K. Familial nonhemolytic jaundice: constitutional hepatic dysfunction with indirect van den Bergh reaction. *Arch. Int. Med.* **67:**259-285, 1941.
44. Krarup, N. B., and Roholm, K. Histologic studies by means of liver biopsy in intermittent jaundice of young persons. *Ugeskr. f. laeger.* **103:**72-75, 1941.
45. Weech, A. A., Vann, D., and Grillo, R. A. Clearance of bilirubin from plasma. Measure of excreting power of liver. *J. Clin. Investigation* **20:**323-332, 1941.
46. Dameshek, W. "Target cell" anemia. Anerythroblastic type of Cooley's erythroblastic anemia. *Am. J. M. Sc.* **200:**445-454, 1940.
47. Wintrobe, M. M., Matthews, E., Pollack, R., and Dobyns, B. M. Familial hemopoietic disorder in Italian adolescents and adults resembling Mediterranean disease (thalassemia). *J. A. M. A.* **114:**1530-1538, 1940.
48. Strauss, B. B., Daland, G. A., and Fox, H. J. Familial microcytic anemia: observations of six cases of blood disorder in an Italian family. *Am. J. M. Sc.* **201:**30-34, 1941.
49. Eliel, L. P., and Bayles, T. B. Microcytic, hypochromic anemia, associated with splenomegaly and refractory to treatment: report of a case. *New Eng. J. Med.* **225:**134-136, 1941.
50. Dameshek, W. Unpublished data.
51. Bohrod, M. G. The significance of target cells in anemia. *Am. J. M. Sc.* **202:**869-874, 1941.
52. Barrett, A. M. A special form of erythrocyte possessing increased resistance to hypotonic saline. *J. Path. & Bact.* **46:**603-618, 1938.
53. Bauer, J. Sickle cell disease: pathogenic, clinical and therapeutic considerations. *Arch. Surg.* **41:**1344-1362, 1940.
54. Danford, E. A., Marr, R., and Elsey, E. C. Sickle cell anemia, with unusual bone changes. *Am. J. Roentgenol.* **45:**223-226, 1941.
55. Hughes, J. G., Diggs, L. W., and Gillespie, C. E. The involvement of the nervous system in sickle-cell anemia. *J. Pediat.* **17:**166-184, 1940.
56. Skoog, A. L. Cerebral complications in sickle cell anemia. *South. M. J.* **33:**714-721, 1940.
57. Cummer, C. L., and LaRocco, C. G. Ulcers of legs in sickle cell anemia. *Arch. Dermat. & Syph.* **42:**1015-1039, 1940.
58. Diggs, L. W., and Pettit, V. D. Comparison of methods used in detection of sickle-cell trait. *J. Lab. & Clin. Med.* **25:**1106-1111, 1940.
59. Sherman, I. J. The sickling phenomenon, with special reference to the differentiation of sickle cell anemia from the sickle cell trait. *Bull. Johns Hopkins Hosp.* **67:**309-324, 1940.
60. Scriver, T. B., and Waugh, T. R. Studies on a case of sickle cell anemia. *Am. J. Dis. Child.* **40:**922, 1930.
61. Fox, C. L., Jr., and Ottenberg, R. Acute hemolytic anemia from sulfonamides. *J. Clin. Investigation* **20:**593-602, 1941.
62. Emerson, C. P., Ham, T. H., and Castle, W. B. Hemolytic action of certain organic oxidants derived from sulfanilamide, phenylhydrazine and hydroquinone. *J. Clin. Investigation* **20:**451, 1941.
63. Farrar, G. E., Jr., Burnett, W. E., and Steigman, A. J. Hemolysinic anemia and hepatic degeneration cured by splenectomy. *Am. J. M. Sc.* **200:**164-172, 1940.
64. Sterner, L. G. Ein Fall von akuter hämolytischer Anämie vom Ledererschen Typ. *Acta paediat.* **28:**196-206, 1941.
65. Levine, P., Katzin, E. M., and Burnham, L. Isoimmunization in pregnancy: its possible bearing on etiology of erythroblastosis foetalis. *J. A. M. A.* **116:**825-827, 1941.
66. Singer, K., and Dameshek, W. Symptomatic hemolytic anemia. *Ann Int. Med.* **15:**544-563, 1941.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28091

PRESENTATION OF CASE

A fifty-two-year-old Canadian architect was admitted to the hospital because of dyspnea of several months' duration, following a series of neuromuscular symptoms extending over a period of years, for which he had been seen in the hospital previously.

About ten years before this last entry, there was gradual onset of numbness and tingling in the hands and feet, sensation remaining unimpaired. About six years later, the patient began to have progressive difficulty in walking, and became unsteady on his feet. Four months after this, he was admitted to the hospital, when the pupils were irregular and unequal, and reacted to distance though not to light. There was slight drooping of the upper lids. The legs appeared small, but not definitely atrophied. Deep tendon reflexes could not be obtained in arms, knees or ankles. Vibration sense was absent in the malleoli. Physical examination was otherwise negative. The blood Hinton reaction was negative. The cerebrospinal fluid showed a total protein of 80 mg. per 100 cc., a gold-sol curve of 0012210000, a negative Wassermann reaction and negative microscopy and dynamics. Other laboratory studies were negative. After discharge from the hospital, the patient was given various forms of arsphenamine treatment, which was discontinued because of severe reactions. The symptoms remained stationary for a few months. A right-foot drop then developed, requiring the use of a cuff about the foot, wired to a cuff about the calf, as an aid in walking. The right arm and right leg gradually became increasingly atrophic.

Eleven months before the last admission, the patient experienced unusual dyspnea and prostration, in the course of a coryza lasting several days. A similar attack, lasting three days, occurred seven months later. The dyspnea appeared to be paroxysmal, and was unassociated with any disturbance of heart action. A physician prescribed coramine. The patient went to the White Mountains for a short vacation, and returned after a week, complaining that the slight change in altitude had brought on a return of the dyspnea, with a dry cough. He had a rise in afternoon temperature to 99 or 100°F. His physician noted a distinct expiratory murmur over the middle of the right lung, posteriorly, without rales or areas of dullness. The blood pressure was 110 systolic, 90 diastolic. A roentgenogram of the chest showed old apical tuberculosis on the right, with apparently enlarged lymph nodes at the hilus. Ten days before entry, there was rapid progression of the attacks of dyspnea, and the patient began to lose strength. His cough continued to be unproductive. He had no chills, sweats or chest pain. The blood pressure was 90 systolic, 70 diastolic, at this time. On the advice of a consultant, he was readmitted to the hospital.

The patient's father died of tuberculosis at forty-six years of age. The patient himself, when fifteen years old, spent a year at rest because of a suspicion of tuberculosis. Subsequently, the patient had never been vigorous, although he was seldom sick in bed. He had lived for two years in the Philippine Islands. Exposure to syphilis was denied. Shortly before the onset of the respiratory symptoms, an employee with whom he had worked in close contact for years was diagnosed as tuberculous.

On admission, the patient appeared well developed and nourished but somewhat dehydrated. The lips, fingers and upper chest were cyanotic. The veins of the neck and upper extremities were distended. The lower extremities were pale and cool. The heart was slightly enlarged. The pulmonic second sound was moderately loud, and there was a fairly loud systolic murmur, heard best over the lower half of the heart and toward the apex. There was dullness, with bronchial breathing, over the upper sternum, and a few fine rales at each base. The liver edge was palpable four or five fingerbreadths below the costal margin. There was slight pitting edema over the sacrum, but not in the extremities. The neurologic status was not reviewed at this time.

The temperature was 99°F., and the pulse was 90 and weak but equal in each wrist. The respirations were 20, without cough or wheeze. The blood pressure was 80 systolic, 40 diastolic.

Examination of the blood showed a red-cell count of 4,780,000 with 13.6 gm. hemoglobin, and a white-cell count of 21,000 with 78 per cent polymorphonuclears, 9 per cent small lymphocytes, 12 per cent monocytes and 1 per cent eosinophils. The blood Hinton reaction was negative. The nonprotein nitrogen was 33 mg. per 100 cc.

Roentgenologic examination of the chest showed marked enlargement of the pulmonary vessels toward the hilus, but not distally, with weak pul-

sations. The lung fields showed mottled and linear areas of increased density. There was questionable dilatation of the right ventricle.

An electrocardiogram showed right-axis deviation. All complexes were inverted in Lead 4, with prominent P waves.

The patient continued dyspneic. He was given oxygen, and a phlebotomy of 300 cc. was performed, without appreciable effect. Death occurred from respiratory failure on the third hospital day.

Differential Diagnosis

Dr. J. H. Means: This somewhat complicated story divides itself fairly well into two chapters, which I might consider to some degree separately. The history ten years previously and continuing down to four years previously, when the patient was in the hospital for study, was characterized by some paresthesias and later by the development of difficulty in walking, unsteadiness on the feet and irregular, unequal Argyll-Robertson pupils, with ptosis of both eyelids, absent tendon reflexes and absent vibration sense; I cannot reconcile this with anything but tabes, perhaps of a rather burnt-out sort. There is no evidence to point to a diagnosis of combined system disease and no suggestive blood picture, nor is the story typical of such disease. The Argyll-Robertson pupil is fairly pathognomonic. The irregularity may likewise be due to syphilis. The blood Hinton reaction was negative. That does not signify anything because it is often negative in long-standing tabes of an inactive sort. The protein was elevated, and the gold-sol curve was not very impressive, but it had a hump in the middle that would go with tabes satisfactorily, so that I cannot get away from that diagnosis, and I therefore make it without more discussion.

Later, however, there were neurologic findings that were not consistent with tabes. Motor phenomena came on after some arsenical treatment, to which the patient responded poorly. A right-foot drop developed, which required apparatus to permit him to walk, and he developed muscle atrophy in the right leg and also in the right arm. This distribution of atrophy in the right arm and leg sounds as though he had had a cerebral lesion, but since the rest of the picture was very much more like that of a peripheral neuritis I must confess that I am puzzled. However, I believe that the foot drop was almost certainly due to peripheral neuritis. Of course, the reflexes were absent anyway because of tabes. I do not know what would happen to reflexes in the event that a tabetic patient, with no reflexes, developed hemiplegia from a cerebral accident. What would happen?

Dr. Charles S. Kubik: The reflexes would remain absent.

Dr. Means: Then we cannot say that this patient did not have some cerebral lesion, but I think it is most unlikely, and we have no proof. What I think he had was an arsenical neuritis, which gave him foot drop. Why the right arm rather than the left or some other part was also involved, I cannot say. It may have been just chance. At any rate, I am unable to go any farther with the neurologic diagnosis. I leave it there.

The symptoms in the second period, which began eleven months before entry, instead of pointing to the nervous system, involve the circulatory system in a somewhat puzzling fashion. Certain features about the symptomatology suggest an upper mediastinal pressure syndrome. We are told that the neck veins were dilated and that a venipuncture was performed in the hope of giving relief, and we are also told that the patient was cyanotic in his upper extremities, the upper chest, neck and face, but nowhere else. These manifestations go with an upper mediastinal pressure syndrome, and I dare say that the dyspnea might also be consistent. But other things do not fit that interpretation so well. There is some evidence of edema and congestive failure with a large liver, and perhaps an upper mediastinal pressure syndrome is not the most likely explanation.

Let us consider the various symptoms. As I read the second chapter, I was impressed with the following symptoms. In the first place, the paroxysmal dyspnea was unassociated with disturbance of the heart action. I am interested in the story that, after getting better, the patient became worse when he went to a somewhat higher altitude; this suggests that a relative oxygen want played a part in the dyspnea. The progressive fall in blood pressure may be significant — at any rate, it is very striking. It started as 110 systolic, 90 diastolic, and dropped to 80 systolic, 40 diastolic, shortly before he died. I am also impressed with the fact that there was some evidence of infection: a temperature of 100°F. and a leukocytosis that requires explanation. I am interested that there was evidence of old tuberculosis, with apical and lymph-node involvement. I am rather impressed with the progression of the attacks of dyspnea and the evident marked loss of strength.

The matter of tuberculosis might be discussed for a moment at this point. The patient had been suspected of having it in childhood. He

FRANKLIN SQUARE HOSPITAL LIBRARY

showed obsolete tuberculosis by x-ray study. The exposure to the person with whom he worked in close contact does not impress me as being significant, because it is unlikely that one would catch tuberculosis at his age — he was beyond the age when one contracts new tuberculosis. He had been working with this person for years, however, but we do not know how many. I fancy he had tuberculosis before he established this contact, so that it is not of great importance.

It is to be observed that the patient denied exposure to syphilis, but I believe that he had had it. I do not see how we can escape that conclusion.

When he came into the hospital, the significant signs were the high venous pressure, the loud pulmonic second sound and the loud systolic murmur, heard best over the lower half of the heart and toward the apex. It did not go out to the axilla, like a mitral murmur, and seems to have been more in the region of the pulmonary area. He also had dullness, with bronchial breathing, over the sternum. Dullness there suggests dilatation of the great vessels or a mediastinal mass, or something of that kind that would go with the upper mediastinal pressure syndrome. There may have been some element of upper mediastinal pressure in addition to another factor that produced the rest of the picture. Later, the patient had a palpable liver and pitting edema, and the blood pressure dropped. The laboratory work, except for the leukocytosis and perhaps a monocytosis, does not help us much. The right-axis deviation is of interest. The x-ray examination described — I have not seen the films — some changes in the pulmonary vessels and some enlargement of the heart in the region of the right ventricle.

May we see the x-ray films and try to pull all this together?

Dr. Aubrey O. Hampton: At the first examination, one might on first inspection call these enlarged lymph nodes at the lung roots, particularly since the patient had evidence of old tuberculosis, but in this Bucky film one can see that they are blood vessels. The blood vessels of the lung roots are grossly enlarged, and they end rather abruptly in the middle of the lungs.

Dr. Means: Can you tell whether they are arteries or veins?

Dr. Hampton: They are probably pulmonary arteries.

The film also shows a few rather short linear scars in the lungs scattered around in queer places below the site of the old tuberculosis; these scars were not present at the examination a month before.

Dr. Means: Did the patient have emphysema?

Dr. Hampton: The diaphragm is relatively low, but there was no note of limitation in excursion.

Dr. Means: What about the upper mediastinum? Is there a mass of any kind?

Dr. Hampton: No; the trachea is in normal position, and the main bronchi are normal.

Dr. Means: Is there any stenosis?

Dr. Hampton: No. This film shows a definite change in the bases of the lungs, as compared with those taken at the examination a month before. It looks like pulmonary edema, in addition to poorly outlined areas of consolidation.

Dr. Means: Are these areas of fibrosis?

Dr. Hampton: I think that this upper shadow is fibrous because of old tuberculosis; the remainder does not appear to be. There are no blebs. The heart is definitely enlarged. The supposition that the enlargement was right ventricular is, however, based on fluoroscopy.

Dr. Means: Is there any reason to give up that idea?

Dr. Hampton: None at all.

Dr. Means: It seems to me that the high venous pressure, the cyanosis, the right-sided enlargement, the electrocardiogram showing right-axis deviation, and the engorgement of the pulmonary arteries by x-ray studies, indicating high arterial pressure in the pulmonary artery, all fit the interpretation of this case as one of chronic cor pulmonale. The upper mediastinal pressure syndrome I should be inclined to give up because we have not found, by x-ray or other examination, evidence of anything that could produce upper mediastinal pressure. Why only the upper half of the body was cyanotic, I cannot explain. Frankly, that puzzles me a good deal.

Why did the patient have cor pulmonale, and did he have anything else? I should like to throw in, not as a diagnosis but just by way of discussion, an idea that occurred to me as I went over this history. One of the conspicuous symptoms was paroxysmal dyspnea. One usually finds paroxysmal dyspnea in hypertension. This man was hypotensive. He had these paroxysms of dyspnea, and I do not believe that they were asthmatic because there is nothing to go with that. The low blood pressure, the prostration and the paroxysms of dyspnea are very impressive, and they make me think of an adrenocortical insufficiency, particularly since the last came on at a time when the patient did not have other cardiac symptoms, and I remember being told by one of my teachers that he had seen very striking paroxysms of dyspnea in Addison's disease. I looked through several textbooks of medicine and could

find nothing whatever about it. The Addisonian crises that are somewhat like shock are described, but nothing is said about paroxysmal dyspnea. I therefore called my teacher on the telephone,—it was Dr. William H. Smith,—and he said, "You are entirely correct; I have seen Addison's disease with symptoms of severe attacks of paroxysmal dyspnea." He said that Dr. George Sears had also seen it and had told him about it. I cite them as authorities that in Addison's disease one does get paroxysmal dyspnea. I am not prepared to say that this patient had Addison's disease, but I shall be interested in what is found in the adrenal glands, and if anything is found there pathologically I shall be satisfied; if it is not, I shall not be disappointed, because it is a long shot.

How can we put these findings together on one etiology? The tabes was due to syphilis, of course. Could the rest of it have been due to syphilis? Well, it could. Cor pulmonale occurs in Ayerza's disease, which is a type of syphilitic endarteritis of the pulmonary vessels. That is a possible explanation. It is also stated in the textbooks that sometimes syphilis affects both adrenal glands and produces adrenocortical insufficiency or Addison's disease, so that syphilis probably could explain everything except the peripheral neuritis, which is explained by the antisyphilitic treatment. However, we know that the patient also had tuberculosis,—we have evidence by x-ray examination and by the history,—and that he had been running a fever; the high white-cell count could have been due to active tuberculosis. Dr. Paul D. White,* in his book, does not mention tuberculosis as a primary cause of cor pulmonale, but he does mention fibrosis. I suppose that tuberculosis produces fibrosis of the lungs; it certainly causes fibroid phthisis. This patient apparently did not have a serious enough process to cause cor pulmonale, but this is definitely a recognized possibility. Dr. White also mentions pneumoconiosis and silicosis as giving rise to fibrosis, which could produce cor pulmonale. I do not know that this man had any such exposure, so that I do not know which etiology is most likely here. We can explain everything on one etiology if we say this was syphilis, but on the doctrine of chances it is somewhat more likely to be on a tuberculous basis. I therefore summarize by offering as diagnoses, with a certain amount of trepidation: tabes, old and inactive; arsenical peripheral neuritis, with toe drop—I do not know if he still had it at the last entry because they did not mention a neurologic examination; cor pulmonale, with congestive failure the cause of death; some form of pulmonary fibrosis; and, possibly, adrenocortical insufficiency, more likely due to tuberculosis than to syphilis. I do not believe that one need mention cancer, although the adrenal glands are sometimes involved by a malignant process. I cannot find any evidence of cancer, so I think that it can be ruled out.

*White, P. D. *Heart Disease*. 931 pp. New York: Macmillan Company, 1931. Pp. 404-409.

DR. DONALD KING: I saw this man in consultation with Dr. Kite. On the basis of this first film, as Dr. Hampton said, I thought he probably had enlarged lymph nodes at the hilus. I sent him in with the idea that it might be lymphoma and that x-ray treatment might relieve the pressure.

I do not believe that the cyanosis of the upper part of the body, as distinguished from the rest of the body, was very marked.

DR. TRACY B. MALLORY: Sometimes, in simple cases of emphysema, it is more marked in the upper half of the body than in the lower half; I do not know why.

DR. KING: The roentgenologist who went over the films and did the fluoroscopy said that the shadows were pulmonary arteries and not lymph nodes, and that settled that. Then the question came up concerning the condition in the vascular bed in the lungs. Experience has shown that it is difficult to distinguish between plain pulmonary arteriosclerosis without narrowing of the lumen, obliterating endarteritis and thrombi. Dr. Bland saw this man in consultation. I forget which of these diagnoses he chose, but I think that it was obliterative endarteritis.

DR. EDWARD F. BLAND: I chose that, but I think we overlooked the leukocytosis and the paroxysms that Dr. Means has brought out. I might say that we saw him just before he died, and we did not have quite the problem that Dr. Means had in dealing with the past history. He was a very ill man, with obviously extreme cor pulmonale, distended neck veins, congested liver and the x-ray findings described; when it was all added up, we chose between two possibilities—obliterative endarteritis and thrombi.

DR. KING: The patient probably did not have pulmonary fibrosis from the x-ray standpoint.

DR. HAMPTON: I do not believe he had enough to produce cor pulmonale. It is chiefly confined to the upper lobes. The lower lobes are very good. The change in the bases of the lungs over a period of a month are further evidence that the process was more acute.

DR. PAUL D. WHITE: What was your second choice, Dr. Bland,—thrombosis of the pulmonary vessels based on emphysema?

DR. BLAND: We could not find any source for emboli.

DR. HAMPTON: These shadows are quite like those of pulmonary infarcts.

DR. WALTER C. KITE: I think it has not been emphasized that all the neurologic symptoms were unilateral, all on the right side. The cyanosis and the dilatation in the neck did not develop until five days before death. This man was in the office at work one week before Dr. King first saw him.

DR. KUBIK: When this patient was studied here, about three and a half years before he died, a presumptive diagnosis of tabes dorsalis was made. At that time, there was not much weakness. The patient had been complaining of numbness or paresthesia, and there was some analgesia, as well as impairment of vibratory and position sense. The Argyll-Robertson pupils influenced us a great deal, as they did Dr. Means. The later course, marked by the development of foot drop, and the marked weakness, with some atrophy, did not fit in with tabes. I believe that the patient was seen later at the Boston City Hospital, where a diagnosis of peroneal muscular atrophy was made. When he was here, we did think of the possibility of hypertrophic interstitial neuritis, but could not find any hypertrophy of the peripheral nerves and concluded it probably was not that.

CLINICAL DIAGNOSES

Pulmonary endarteritis.
Cor pulmonale.
Heart failure, right-sided.
Tabes dorsalis?

DR. MEANS'S DIAGNOSES

Chronic cor pulmonale.
Congestive failure, right-sided.
Pulmonary fibrosis (? type).
Tabes dorsalis, old.
Arsenical neuritis, old?

ANATOMICAL DIAGNOSES

Degeneration of spinal-nerve roots.
Secondary degeneration of posterior columns.
Thrombosis, left popliteal vein, old.
Embolism and thrombosis of pulmonary arteries, old and recent.
Cor pulmonale.
Infarcts of lungs, healed.
Chronic passive congestion.
Ascites.
Pulmonary tuberculosis, inactive.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The post-mortem examination showed a considerably enlarged heart; nearly all the enlargement was on the right side, the right ventricle was nearly twice as capacious as the left, and in spite of the dilatation, it measured 7 mm. in thickness. The pulmonary arteries showed clots of all ages, some quite fresh and some evidently very old, completely organized and extensively recanalized. These were present in the major and intermediate-sized arteries, and the small arterioles throughout the lung were entirely normal. The picture suggested to us multiple embolism, with perhaps secondary retrograde thrombosis and primary pulmonary endarteritis. As a possible source for this, there was an extensive old thrombophlebitis of the left iliac vein. Will you continue with the neurologic findings, Dr. Kubik?

DR. KUBIK: There was marked degeneration of the calf muscles, presumably secondary to disease of the anterior spinal roots or of the spinal roots and anterior horn cells. Both anterior and posterior spinal roots of the cauda equina were enlarged. Many of them were two or three times the normal size. Microscopic sections showed that the enlargement was due to interstitial tissue; the fibers were actually diminished in number. The remaining ones were in process of degeneration. There was degeneration in the posterior column, which, I should say, was secondary to degeneration of the posterior roots. I am not altogether sure about the findings in the anterior-horn cells. Many of them exhibited changes that were unquestionably secondary to the degeneration of the anterior roots (axonal reaction), but I could not be sure that there was not also some primary degeneration. It will require further study to establish a diagnosis. Peroneal muscular atrophy (Charcot–Marie–Tooth disease) is a possibility, and perhaps hypertrophic interstitial neuritis also has to be considered, even though there was no hereditary or familial history.

DR. MEANS: What were the Argyll-Robertson pupils due to?

DR. KUBIK: I cannot answer that. The midbrain has not yet been examined.

DR. MEANS: Did your neurologic examination exclude ordinary tabes? You told us that you did not know what to call it, but can you say it is not tabes?

DR. KUBIK: Almost certainly not. In tabes, the anterior roots are of normal size, and the posterior roots are very small.

DR. MEANS: Was there any evidence of tuberculosis?

DR. MALLORY: There was inactive apical tuberculosis, not progressive.

DR. MEANS: Were the adrenal glands normal?

DR. MALLORY: Yes.

CASE 28092

PRESENTATION OF CASE

First admission. A sixty-three-year-old housewife was admitted to the hospital because of a fainting spell.

She had suffered recurrent episodes of abdominal pain for many years. These attacks, which were described as crampy, colicky and associated with "gas," started in the left upper quadrant, and occasionally radiated over the lower ribs or down the left arm and to the left subscapular region. The pain was never substernal. There was no nausea or vomiting, and the bowels had always been regular. In the year before entry, the discomfort seemed to follow exertion, although this was not always so. The patient was able to relieve the pain by raising or swinging her arm, or by taking nitroglycerin. At times, she took bismuth and restricted her diet, and passed several weeks without pain. On the evening of admission, an attack came on while the patient was attending a concert. She took a tablet of nitroglycerin, and shortly afterward fainted.

The family history was irrelevant, and the past history complicated. The patient had had severe varicella when thirty-nine years old. At forty-one, she had had the uterus removed for prolapse. Two years later, the gall bladder had been removed for "pain"; gallstones were found at the operation. Hemorrhoids were removed at the age of fifty-one, yet the patient noted occasional bright-red blood in the stools in the year preceding entry. Eight months before admission, roentgenographic examination, including a barium enema and a gastrointestinal series, showed "diverticulosis of the large bowel."

Physical examination showed an obese woman in no distress. The chest showed evidence of old rickets. The heart was of normal size, with a very soft systolic murmur of the apex, and a loud, ringing aortic second sound. The lungs were clear. There was slight, diffuse tenderness in the abdomen, most evident in the left upper quadrant. The liver edge was palpable one or two fingerbreadths below the costal margin.

The temperature was 97°F., the pulse 75, and the respirations 24. The blood pressure was 160 systolic, 90 diastolic.

Examination of the blood showed a white-cell count of 5900. The urine showed a + test for albumin, with 50 white cells per high-power field in the sediment.

An electrocardiogram showed sinoauricular bradycardia, with a rate of 50. The P waves and PR intervals were normal. There was slight slurring of the QRS complexes, and marked left-axis deviation, with inversion of all complexes in Lead 3.

The patient was discharged on the second day.

Second admission (nine months later). Seven months after discharge, the patient fell downstairs and fractured her left shoulder. Because of this injury, she lay on her right side frequently, a position that seemed to bring on the customary attacks of abdominal pain. A month later, the right ankle was broken in another fall. A month after this, one of the episodes of abdominal discomfort was followed abruptly by radiation of terrific, "tearing" pain downward over the whole left side into the pelvis. The patient felt nauseated and dizzy, and vomited. There were no chills or fever. Nitroglycerin afforded no relief. After an hour and a half, a physician gave her a hypodermic injection. The severe pain went away gradually within half an hour, but an ache was then noted in the arms below the shoulders. Then, there was gradual onset of numbness and weakness in both legs, progressing to anesthesia, and paralysis within two hours. The patient was unable to urinate or defecate. In retrospect, the patient stated that her left leg had seemed colder than the right for several months before this attack.

On re-examination, the patient again appeared in no acute distress. The heart and lungs were essentially as before. The abdomen was distended. The liver edge lay two to three fingerbreadths below the costal margin. There was total loss of sensation in the lower extremities and abdomen below a level corresponding approximately to that of the insertion of the diaphragm. The upper limit of this area of anesthesia shaded off gradually rather than sharply. The skin over the region involved was of normal color. Voluntary movements of the lower extremities were abolished. Deep tendon reflexes and abdominal reflexes were absent. Stimulation of the soles of the feet produced slow mass flexion and extension reflexes of the whole lower extremities.

The temperature was 100.5°F., the pulse 65, and the respirations 20. The blood pressure was 110 systolic, 60 diastolic, in each arm.

Examination of the blood showed a white-cell count of 9200 with 83 per cent polymorphonuclears, and a red-cell count of 4,000,000 with 12.2 gm. hemoglobin. The serum protein was 5.5 gm.

per 100 cc. The urine showed a + test for albumin, with occasional red cells in the sediment.

An electrocardiogram was quite similar to that obtained on the first admission, except for increase in amplitude of T_2 and T_3, without, however, any characteristic shape.

A roentgenogram of the thoracic spine showed no evidence of vertebral disease. The entire thoracic aorta was tremendously enlarged. The aortic knob, 10 cm. in diameter, displaced the trachea toward the right. There was calcification in the inferior rim of this knob, and a line of calcification in the wall of the descending aorta, lying well out toward the axillary line. The heart shadow showed prominence in the region of the left ventricle. The lung fields were clear.

Lumbar puncture yielded clear colorless fluid under initial pressure of 145 mm. Microscopic examination showed 454 red cells and 1 white cell per cubic millimeter. The total protein was 52 mg. per 100 cc. The gold-sol curve was 1233411000. There was insufficient fluid for a test of the Wassermann reaction.

On the second hospital day, the temperature fell to 98°F., and the pulse and respirations continued as before. The patient felt prickling in the legs and feet, especially on the right, but there was a slow further return of protopathic sensation. Bilateral Babinski plantar responses gradually appeared. Subsequent roentgenograms of the chest showed essentially no change. From time to time, there were transient elevations of temperature to 100°F. Tidal drainage of urine by catheter was maintained. There was intermittent bacilluria, which responded fairly well to sulfadiazine therapy. The patient was discharged after ten weeks, unimproved.

At home, the slow return of sensation continued, but there was no return whatever of motor control. The patient continued to have frequent bouts of pain, which appeared to originate in the left upper quadrant but radiated to the region of the left scapula and, on one occasion, to the right shoulder. The pain was often severe enough to make her break out in a perspiration. It could sometimes be relieved by lying on the left side. Relief from the pain was sometimes accompanied by an audible gurgling in the left flank. Two months after discharge, the patient awoke one morning with severe knifelike pain about her left shoulder and under her left scapula. She felt faint and vomited. The pain was gradually relieved after a hypodermic injection of morphine. In the late afternoon of the same day, the pain returned, and the patient rapidly went into severe shock and gradually became comatose. She died five hours after this second attack of pain.

Differential Diagnosis

Dr. Francis R. Dieuaide: We have an elderly woman who had two sets of attacks of pain. One of these comprised colicky pain, which radiated usually into the left upper arm and to the left shoulder and was said to have been present for many years. There were two major episodes of extreme pain, the first of which is described as "tearing," along the left side down to the pelvis. It grew out of one of the attacks of the previous series. It was associated with paraplegia. The second attack was knifelike pain about the left shoulder and under the scapula, followed by death in five hours. These two discrete attacks strongly suggest pain of vascular origin. We also know that there were marked changes in the vessels in the x-ray picture. As to the paraplegia, we are given no sign of interference with circulation in the legs. On the whole there is little doubt that the difficulty was of cordal origin. There were two recent fractures. The question might be raised whether they were pathologic fractures and whether the patient had a neoplasm somewhere, but there is no evidence of that and we are directly told that there was no sign of fracture in the vertebral column. I suppose one should also raise the question whether the difficulty might have been due to metastases in the cord itself, but there is no reason to think of that in the face of the other information; furthermore, we must note the improvement in sensory function, which apparently was quite good, although there was no return of motor function. Everything considered, I think one might easily come to the conclusion that these cord changes were probably due to a vascular disturbance. The two major attacks of pain might possibly suggest coronary pain — associated with myocardial infarction, perhaps; but the description is somewhat peculiar, especially the radiation in the first attack to the pelvis. Such radiation happens occasionally, although rarely. Coronary difficulty offers no explanation for the cord changes. The blood pressure was well sustained, although it did fall somewhat. The electrocardiogram was normal, except for sinoauricular bradycardia. This is very much against a diagnosis of coronary occlusion with myocardial infarction.

An aneurysm of the ordinary saccular sort might possibly account for the recurrent pain, but I do not believe that such an aneurysm could account for the two discrete attacks described. We have no evidence for syphilitic aneurysm: no positive blood or cerebrospinal-fluid Wassermann reaction. The spinal fluid was essentially normal. It was contaminated with a little blood, that is, enough

to produce the gold-sol changes, even though the fluid was colorless.

Of course, this might have been an arteriosclerotic aneurysm; the patient was an elderly woman, and that is a possibility. Furthermore, the calcification in the x-ray pictures speaks directly for that because calcification of that sort is not likely to be present in syphilitic aortitis. The blood pressure speaks somewhat for an arteriosclerotic process. Then we have dissecting aneurysm. The description of the first attack fits very well, I think, into the usual description of dissection, although arm radiation is not nearly so common as it is in myocardial infarction. It is, however, described in some cases; I do not believe that it is against the diagnosis. The maintenance of blood pressure is in favor of it, and the cord changes are particularly in favor of it.

May we see the x-ray films?

DR. TRACY B. MALLORY: There is no radiologist present.

DR. DIEUAIDE: I hesitate to say just what this shadow is, but it is evidently the outline of a vascular swelling of some sort, derived from the aorta and extending far to the left. I doubt if, at a distance, one can see the calcification, but there is a good deal of it spread out in a large semicircular arc well to the left of and below the usual site of the aortic knob. With these x-ray films, in addition to the story, one would, I think, be going out of the way not to concentrate on dissecting aneurysm.

In recent years, we have heard a great deal about dissecting aneurysms in aged people, more commonly perhaps in men, but still not rarely in women. The dissection frequently occurs after exertion, but not necessarily. It is sometimes symptomless, a double aorta being found only by post-mortem examination. The blood pressure is usually relatively maintained in patients who do not succumb. I am inclined to think that this patient had dissection of the ordinary type, based on media necrosis cystica.

The cord changes are of special interest in connection with dissecting aneurysm, if we are right about the diagnosis. They have been recently emphasized by Tuohy et al.,* who stressed the patchy, transient character of the symptoms, and the frequent occurrence of coldness and numbness. The changes described here are severer. We are interested especially in the persistent, complete loss of motor function. I have no explanation for that. I am sure that someone else will be able to tell us about the circulation of the lower cord. As I understand it, it is a little more vulnerable than circulation of the upper cord, because blood is supplied to the upper part by the vertebral arteries, whereas the lower cord has only the branches of the aorta, the intercostal and sacral arteries. If this diagnosis is correct, the lesion should have extended down into the abdomen so that it cut off the blood supply of the lower part of the cord. At the same time, other vessels might have been affected, such as the renal artery. We have no particular evidence of that in this case.

The second attack of pain on the last day speaks for rupture of the dissection. Dissection usually begins in the upper mediastinum. If the patient had a dissection, since there was pain about the left scapula, I should first think of the mediastinum as the site of the rupture.

The preceding series of attacks offer me some difficulty. The attacks for many years were centered in the left upper abdomen, a somewhat unusual site. Did the patient have diverticulosis? In any event, I do not think chronic diverticulitis is a likely explanation. The gurgling that occurred when the patient had relief of pain does not mean much to me. The pain might suggest a second serious lesion, such as carcinoma of the colon, but this is unlikely. I suppose one should mention diaphragmatic hernia. The pain is quite permanent for that, and we ought to be able to see a hernia in the x-ray film. The patient apparently acquired a urinary-tract infection, but these attacks do not sound much like renal pain. The radiation was upward instead of downward, as it usually is in renal pain. Were they attacks of anginal pain? The reasons mentioned before are still against that. Relief by nitroglycerin does not prove anything. Relief by swinging the arm is also rather against angina. I think that the patient must, of course, have had an antecedent aneurysm before the dissection, an unusually large one to be caused by atheroma. Somehow, these attacks of pain were produced by this aneurysm, which I should guess to have been in the first portion of the descending thoracic aorta. So that I think the patient had the following conditions: an old arteriosclerotic process with hypertension, although there is not much evidence of that, and an unusually large arteriosclerotic sac—perhaps I am passing up a chance to make a diagnosis of syphilitic aneurysm, but I do not believe so; a dissecting aneurysm, which went all the way to the neighborhood of the bifurcation of the aorta but not through it; and something like myelomalacia of at least the lower spinal cord, which seems to have affected the pyramidal tract particularly. I suppose there was also cystitis and perhaps pyelitis.

DR. WILLIAM B. BREED: It is strange that no

*Tuohy, E. L., Boman, P. G., and Berdez, G. L. Spinal cord ischemia in dissecting aortic aneurysm. *Am. Heart J.* 22:305-313, 1941.

serologic findings are recorded. I should be interested in knowing what they were.

DR. MALLORY: There was no record of them. The patient's physician checked over his records and also corresponded with other doctors who had seen her. I think it was one of those cases in which each one assumed that the other had done it.

DR. EDWARD F. BLAND: This patient's history and x-ray films were presented at Grand Rounds in the Ether Dome. Some of you may recall it. Dr. Michelsen discussed the cord difficulty. At the time, all were quite convinced that this must be a dissecting aneurysm or some modification of it. I think there was only one dissenting voice, and that was from the pathologist who was present — Dr. Castleman. He wondered if the size of the aorta by x-ray study did not suggest the likelihood of something else than a simple dissection. There were one or two other interesting points that Dr. Castleman raised about the presence of calcification of the aorta. Perhaps he would comment on that now.

DR. BENJAMIN CASTLEMAN: We had never seen a dissecting aneurysm in the presence of marked arteriosclerosis and calcification. Also, the patient did not have hypertension. Although dissecting aneurysms have been recognized on x-ray examination, they do not produce such marked dilatation of the aorta as was seen in this patient.

A PHYSICIAN: I had seen her for three years, and she never had a systolic blood pressure over 160 during that time.

DR. MALLORY: The great majority of the cases that we have seen have had a definite hypertension. One case of Dr. Fremont-Smith's that we presented recently had very little, however.

DR. JOST MICHELSEN: There was little doubt from the onset that the cord lesion was a vascular affair, and the dynamics during lumbar puncture were quite normal. The return of sensation was really very slight — practically none at all. I wonder why Dr. Dieuaide used the term "contamination" of the cerebrospinal fluid. Four or five hundred red cells may be found in cases of vascular obliteration, and are consistent in this case with arterial occlusion, which caused the softening of the cord.

CLINICAL DIAGNOSES

Dissecting aneurysm, with apoplexy of cord at the fifth dorsal segment.
Obesity.
Diverticulosis.

DR. DIEUAIDE'S DIAGNOSES

Extensive atheroma of aorta, with aneurysm.
Dissecting aneurysm.
Myelomalacia of lower spinal cord.
Cystitis or pyelitis?

ANATOMICAL DIAGNOSES

Aneurysm of descending aorta, probably syphilitic, with rupture.
Hemothorax, left.
Arteriosclerosis, severe, aortic and coronary.
Infarction of spinal cord.
Operative scars: cholecystectomy and hysterectomy.

PATHOLOGICAL DISCUSSION

DR. MALLORY: At post-mortem examination, a very large fusiform aneurysm of the descending aorta was found. It began just beyond the arch and extended nearly down to the diaphragm. It was filled with a laminated thrombus, which appeared to cover the mouths of the intercostal arteries; it seemed rather surprising that more of them were not obstructed. The aneurysm had ruptured into the left pleural cavity, which contained about 1500 cc. of blood, and the lung on that side was totally atelectatic. There was no dissection. The question then arose whether this was an arteriosclerotic, senile aneurysm or a syphilitic aneurysm. We have no serologic findings to bear on the point, so that we have nothing to go on but the microscopic appearance of the aorta itself. I do not believe that all members of the department are entirely unanimous as yet, but as I studied it I should have to call it syphilitic. There were marked focal destruction of the elastica in the media, collars of lymphocytes around the vessels in the adventitia, and sizable collections of plasma cells in the adventitia, which I should take more seriously. The ascending aorta was absolutely smooth and normal, and that is unusual in cases of syphilis. Sections of the ascending aorta were entirely normal. If I had to make a decision on the case, I should vote for syphilitic aneurysm. Dr. Kubik will tell us about the cord.

DR. CHARLES S. KUBIK: There was a softening of the cord, beginning at about the fifth thoracic segment and extending down into the midthoracic region. The lower part of the cord was normal.

The cord receives its blood supply from two sources: from the anterior spinal artery, which branches from the vertebral arteries, and from branches of the intercostal arteries. The anterior spinal artery did not provide an adequate blood supply in this case when the intercostals were blocked off by the lesion of the aorta. I do not recall another case like this.

DR. MALLORY: There was enough sclerosis in the coronary arteries for the patient to have had angina. The other possibility is that the attacks of colic were tabetic crises.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established in 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society

Editorial Board

Joseph Garland, M.D. — Stephen Rushmore, M.D.
William B. Breed, M.D. — Henry R. Viets, M.D.
George R. Minot, M.D. — Robert M. Green, M.D.
Frank H. Lahey, M.D. — Charles C. Lund, M.D.
Shields Warren, M.D. — John F. Fulton, M.D.
George L. Tobey, Jr., M.D. — A. Warren Stearns, M.D.
C. Guy Lane, M.D. — Dwight O'Hara, M.D.
William A. Rogers, M.D. — Chester S. Keefer, M.D.

Associate Editors

Thomas H. Lanman, M.D. — Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Walter P. Bowers, M.D., Editor Emeritus
Robert N. Nye, M.D., Managing Editor
Clara D. Davies, Assistant Editor

Subscription Terms: $6.00 per year in advance, postage paid, for the United States (medical students, $3.50 per year); Canada, $7.04 per year, Boston funds; $8.52 per year for all foreign countries belonging to the Postal Union.

Material for early publication should be received not later than noon on Friday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

PROCUREMENT AND ASSIGNMENT SERVICE

In these times of stress, physicians, as well as everyone else, are considering how they can best serve the Nation, and from the point of view of medical service, many factors must be taken into account. There seems little doubt that eventually nearly all male physicians under forty-five years of age who are physically and educationally qualified to enter military service will be inducted, but due regard must also be paid to the medical needs of other governmental agencies, state, county and municipal institutions, nongovernmental hospitals, medical schools, industry and, last but not least, civilian communities.

With all this in mind, the House of Delegates of the American Medical Association, at its meeting in Cleveland last June, recommended to the Government that a procurement and assignment agency for physicians be formed, and on October 31, 1941, the creation of the Procurement and Assignment Service for Physicians, Dentists and Veterinarians, a subdivision of the Office of Defense Health and Welfare Services of the Office for Emergency Management, was authorized by the President. This agency is specifically instructed "to receive from various governmental and other agencies requests for medical, dental and veterinary personnel, to secure and maintain lists of professional personnel available, showing detailed qualifications of such personnel, and to utilize all suitable means to stimulate voluntary enrollment, having due regard for the overall public health needs of the Nation, including those of governmental agencies and civilian institutions." In accordance with the suggestion of the House of Delegates, the Directing Board is composed of five civilian practitioners, — four physicians and one dentist, — the chairman being Dr. Frank H. Lahey, of Boston, president of the American Medical Association.

Owing to the proximity of the creation of the Procurement and Assignment Service and the declaration of war on December 8, the bare skeleton of the necessary working force of the central office in Washington had only been established when it was flooded with requests for personnel from the military services and governmental agencies and for information from physicians, dentists and veterinarians. The demand for personnel resulted in an appeal for physicians who were immediately available for military service, and the response was so satisfactory that these needs have been met. It has been impossible, however, to answer the letters requesting information, and the Directing Board of the Procurement and Assignment Service decided that all existing pertinent facts should be made available to physicians, dentists and veterinarians. Much of this material has appeared from time to time in the *Journal of the American Medical Association* and the state medical journals; but there has been little continuity, and many of the basic regulations have subsequently been changed. Hence, the article in the February 21

issue of the *Journal of the American Medical Association* that describes the functions and activities of the Procurement and Assignment Service, gives recommendations based on current regulations and furnishes additional miscellaneous information should be carefully read by all members of the medical profession.

Subsequent planning for the provision of military personnel and for the protection of nonmilitary medical services demands more facts than are now in the hands of the Procurement and Assignment Service, which consist chiefly of data taken from the questionnaires sent out by the American Medical Association over a year ago. State, district or county and local committees must prepare lists of essential personnel, which are based on the needs of industry, medical schools, hospitals and communities. But what is even more important, exact up-to-date information concerning the status of all physicians must be obtained. Within a few weeks, the Procurement and Assignment Service will forward a questionnaire to every physician, dentist and veterinarian within the United States. Furthermore, this will be accompanied by an enrollment form, whereby the physician, dentist or veterinarian, by signing up with the Procurement and Assignment Service, can express his willingness to help in the present emergency and can indicate his preference for service.

When the questionnaire is received, *all registered physicians, regardless of age, sex, physical condition, educational qualifications and citizenship, should immediately fill it out and return it.* Enrollment is purely voluntary, but in view of the criticalness of the war situation, it is difficult to comprehend how any physician can fail to offer his services to his country — ENROLLMENT SHOULD BE ONE HUNDRED PER CENT!

EXAMINATION OF SELECTEES

UNTIL very recently, selectees have been examined by physicians of the Selective Service boards and, if classed by them as fit for general military service, have been sent within a few weeks to an induction center, whose physicians work directly under the supervision of the Army of the United States. Selectees were sent to the induction centers on the assumption that they were physically and mentally fit and that they would be immediately sworn into the Army and sent to camp. Unfortunately, this was not the case. Approximately 18 per cent of the men were rejected because of the findings of the examiners at the induction centers, yet these men had had, perforce, to give up the positions in which they were employed and returned to their homes without a job and marked, in a way, as unfit. Furthermore, employers did not always distinguish between ability to hold down a civilian job and that to stand the rigors of combat service.

This has all been changed — and for the better. Selectees are examined by their local examining boards only for "gross disqualifying defects." If none are found, the men are, at some later date, sent to an Army examining or induction center. If they are then found to qualify fully for "general military service," they are returned to their homes with such knowledge and with the opportunity of rearranging their affairs before being called to camp some weeks later. If rejected, the causes of their defects are explained in simple language, and they are admonished to consult their personal physicians, if there is such a need. The burden on the Army physicians is, of course, greater, and their task more difficult, but the local-board physicians — who generously donate their services — are relieved of much responsibility, and the selectee is in a far better position to arrange his own private affairs, come what may.

It is further hoped that some form of rehabilitation may find its way, officially, into this program. There are thousands of men with remediable defects who could, with appropriate aid, become fit for general military service and, by the same token, even better qualified to carry on in civilian life. Such rehabilitation is at present voluntary. It may and should become compulsory.

OBITUARY

KENNETH DANIEL BLACKFAN

1883 - 1941

Kenneth Blackfan began his career in medicine in the year 1905 as a country doctor. Eighteen years later he became Thomas Morgan Rotch Professor of Pediatrics, and for another eighteen years he carried his department forward with consummate skill and success. There is no need to recount to this faculty his large services to the Harvard Medical School. But, in order that our admiration of him may be complete, the record of a continuous and hard-won education which brought the country practitioner to a position of high effectiveness in university medicine should be before us.

He was born and spent his boyhood in Cambridge, New York, a pleasantly situated hamlet about forty miles north of Albany. On graduating from the local high school, he entered the Albany Medical School of Union University. During his third year, Richard Pearce came to the school as professor of pathology and bacteriology. Kenneth Blackfan responded to the enthusiasm of this fine student of disease. He begged, and won, permission to work in his laboratory through the following summer. A warm student-master friendship sprang up. This friendship determined his future course in medicine. But not immediately. On receiving his medical degree at the age of twenty-two, he returned to his home town and for the next four years drove about the countryside on the varied errands of a general practitioner. He always recalled those horse-and-buggy years with pleasure, and there are older citizens of that region who still delight in relating therapeutic triumphs of "young Doctor Ken." But there were disturbing visits to nearby Dorset, just over the line in Vermont, where Richard Pearce spent his summers. There he found friendly interest and encouragement, which gradually produced the determination to find out what might lie over the horizon in medicine.

So, in the year 1909, the young country doctor set out for Philadelphia with letters from Richard Pearce. There he was kindly received by Samuel Hamill and David Edsall, and a place was soon found for him as resident-in-charge of a foundling hospital. Kenneth Blackfan thereupon became a pediatrician. Two years later, John Howland, who had accepted the professorship of pediatrics in the newly reconstructed medical school of Washington University, offered him a residency. This was a very large stroke of fortune. It removed the adventurer from his lonely post in the foundling hospital and, after two years in St. Louis, placed him in the group of young pediatricians who assembled around Howland in Baltimore when he succeeded Von Pirquet at Johns Hopkins in the year 1912. Here there was a newly built hospital for infants and children, and laboratory equipment far beyond anything which had yet been given a clinical department in this country. Howland's group used their large opportunity with enthusiasm, and under his wise guidance, the laboratories were from the outset importantly productive. It was the place to be in pediatrics at that time. The most beloved member of this group was the resident physician. No one watched work under way in the laboratories with a more eager interest. And he found time to participate. By way of instance, his work with Dandy on internal hydrocephalus has come to deserve that lofty adjective, classic. His demonstration that dehydration is a much more dangerous feature of diarrheal disease than is the state of acidosis, which Howland and Marriott had just discovered, shifted emphasis from alkali therapy to fluid replacement and produced the basis of our present effective treatment of this chief scourge of infants.

When Kenneth Blackfan reached the age of thirty-seven, he was still a resident. He had held this modest post for eleven years. But he had reached his goal. He knew the existing body of knowledge in his chosen field, he knew its frontiers, and he knew where the paths of progress lay. He was a superb diagnostician and a master of detail of hospital care of patients. Behind all this, four years of countryside practice had given him resourcefulness in use of means at hand and an understanding of the social realities of the physician's task. He was in all respects qualified for the diverse duties of departmental headship. His first commission came in the year 1920, when he was appointed professor of pediatrics at the University of Cincinnati. There he built up his department and guided a large development of hospital equipment with outstanding success. Then in 1923 the fruits of eighteen years of education toward leadership fell to Harvard.

Why did he follow this long and economically narrow path with such serene contentment? This question would have annoyed Kenneth Blackfan. His philosophy was remarkably uncomplicated. There was nothing which could be called ambition, and there was nothing of the *ich dien* complex about him. He had simply discovered a durable delight in his work. The anatomy of this delight did not interest him. He knew an inscrutable phenomenon when he saw one. His modest and conservative use of a fine mind gave

LIBRARY
FRANKLIN SQUARE HOSPITAL

his judgments a great validity and brought him into a high position in the councils of this school. Knowing little of the art of verbiage, he was not a skillful lecturer, but in the wards his teaching of students and of interns was close to perfection. He used the treasures of his experience, not to dazzle by making the diagnosis at a glance, but to point out sound appraisement of obtainable evidence.

A large cause of Kenneth Blackfan's success in leadership was his gentle friendliness. He always made his associates feel that they were his comrades in the enjoyable adventure against disease. Also, he was very brave. Beginning in his later Baltimore years, he suffered a series of physical afflictions which he bore with an unbelievable fortitude. He was friendly and gentle and brave. The simplicity and the sincerity of these traits gave him his great beauty of personality.

J. L. G.
J. H. M.
R. M. S.

A resolution adopted by the Faculty of the Harvard Medical School, January 7, 1942.

* * *

Kenneth Daniel Blackfan, Thomas Morgan Rotch Professor of Pediatrics at the Harvard Medical School, chief of the Medical Service of the Boston Children's Hospital, medical director of the Infants' Hospital, wise counsellor to many, was born in Cambridge, New York, in 1883, the son of a country doctor. He was graduated from the Cambridge High School in 1901 and from the Albany Medical School of Union University in 1905, and after this minimal amount of formal education, became himself a country practitioner. From this realistic postgraduate course in the art of medicine, he emerged four years later, *summa cum laude*.

Turning his back at this point on general practice, he became resident-in-charge at the St. Vincent de Paul Foundling Hospital in Philadelphia, then resident pediatrician at the St. Louis Children's Hospital, then, in 1912, resident pediatrician at the Harriet Lane Home and instructor in pediatrics at Johns Hopkins University School of Medicine. He was still at this post, in 1917, when the first world war stripped the country of its physicians. His associates left him, even to his chief, John Howland; he himself was an officer in the Medical Reserve Corps but, afflicted with corneal ulcers following a Gasserian-ganglion operation, was, of necessity, released from military service.

"They also serve who only stand and wait." Kenneth Blackfan remained in Baltimore and, almost single-handed, with the help of his students, carried the department and the Harriet Lane Home through the war years.

In 1917, he was made an associate and, in 1919, associate professor of pediatrics. The following year he became professor of pediatrics at the University of Cincinnati, where he remained until the call to his last post, with us, in 1923.

Labors fall in good measure upon willing shoulders, and Kenneth Blackfan bore his share of them uncomplainingly, and the honors that sometime accompany them, unassumingly. Among other obligations that he accepted after coming to Boston were, in 1925, the presidency of this society and, for the three succeeding years, membership on its council.

After he had spent those years in the wilderness of private practice, with the intellectual diet of locusts and wild honey that accompanied them, his activities became more diversified, being divided among clinical, investigative and administrative medicine, always with teaching. It is with these four major activities in mind, but with his personality in the foreground, that we do honor to him now and record these simple facts.

> A good tree cannot bring forth evil fruit; neither can a corrupt tree bring forth good fruit.
> Wherefore by their fruits ye shall know them.
>
> *Matthew* VII: 18–20

J. G.

A resolution adopted at a meeting of the New England Pediatric Society on January 14, 1942.

MEDICAL EPONYM

Murphy Button

On October 15, 1892, Professor John Benjamin Murphy (1857–1916) read his first description of this article before the Mississippi Valley Medical Association, and the paper appeared under the title "Cholecysto-intestinal, Gastro-intestinal, Entero-intestinal Anastomosis and Approximation without Sutures (Original Research)" in the *Medical Record* (**42:** 665–676, 1892).

> To overcome these obstacles and thus lessen the risk to the life of the patient, I have devised a mechanical means to dispense with the need of sutures, the necessity of invagination, the possibility of non-apposition, the sloughing through of disks, the digestion of the catgut, the almost unsurmountable difficulties of technique of operation, the prolonged and fatal exposure of the abdominal contents, and the protracted anaesthesia. How much I have accomplished by my labor I desire you to be the judges, after I have demonstrated to you the results of my experiments, and performed for you a gastroenterostomy and an end-to-end approximation of intestine by means of the device I here present to you, to be known as the Anastomosis Button.
>
> R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Obstetric Routines

No one can tell how seriously the national emergency will influence hospital nursing, but much of the refinement that has come to be regarded as necessary will have to be eliminated. It is not at all unlikely that many obstetric services will very seriously feel the shortage of nurses; however, if well-trained and efficient head nurses can be retained, such services can be staffed by younger and less experienced nurses. If this situation eventuates, and something of the sort undoubtedly will, the fewer drugs there are in the medicine cabinets the simpler their administration will be, and the fewer the mistakes made. Furthermore, such a policy will cut down on expense.

Laboratory investigation has proved that skin disinfection at the time of labor can no more adequately, or perfectly, be accomplished than by the use of ether and a 1 per cent iodine solution. The same combination has also been used for a long time, with perfect success, for preparation of the abdomen for laparotomy. The cost of this solution, depending on the market value of alcohol, is about 13 cents a pint. The formula of the solution is as follows: potassium iodide, 1 gm.; iodine, 1 gm.; and alcohol (95 per cent) up to 100 cc. The most economical way of applying the solution is to use a spray. A No. 15 DeVilbiss atomizer, with a nasal applicator, has proved to be satisfactory. For the preparation of the skin, when it is desirable to cause no discomfort, a watery solution of Zephiran is suggested. It is advised that no other solutions for skin disinfection be used in the delivery rooms.

The objection that iodine causes burns and so should not be used has been proved false, over a long experience, especially when such a weak solution is employed. Iodine may cause an occasional burn, but so may other skin disinfectants. Diabetic patients are said to have very sensitive skins; however, in a long experience with diabetic patients, no skin burn of any particular degree has occurred.

Because of the sensitiveness of the skins of some diabetic patients, the use of zinc oxide adhesive tape has been discontinued. Since in a large general hospital the use of zinc oxide tape, for the purpose of holding dressings on surgical wounds, must be a great expense in the course of a year, and since it is imperative that all savings be considered, it is suggested that this practice be discontinued. A gauze roll held in the stay sutures makes a satisfactory dressing.

Many preparations of ergot are on the market. If one standard preparation can be decided on for general use, it will make for a simpler, easier-running service. It is suggested that 1/320-gr. ampules of Ergotrate or Hypoloid Ergometrine be used intravenously and intramuscularly; these cost $21.60 per hundred. Ergotrate or Ergometrine tablets, which cost about 4 cents apiece in thousand lots, are suggested as the sole ergot preparation to be used for oral administration. This routine has already been established in several hospitals in the Boston area.

It is also suggested that, because of the cost, thymol iodide *U.S.P.* be used solely in place of all other, and more expensive, dusting powders.

RETIREMENT

Frank L. Morse, M.D., of Somerville, has recently retired after forty years' service with the Somerville Board of Health. He graduated from Harvard Medical School in 1894, and after three years at the Boston City Hospital, including two years as assistant resident physician at the South Department, was medical and sanitary inspector of the Massachusetts Board of Health from 1898 to 1905 and a district health officer from 1909 to 1915. From 1901 until his retirement from the Somerville Board of Health, he had been in charge of the bacteriologic laboratory, the contagious-disease hospital, contagious-disease control and all other medical work of the Board. He was discharged from active service in the United States Army in 1919, with the rank of lieutenant colonel, and was retired from the Officers Reserve Corps in 1935, with the rank of colonel.

"CHILDHOOD ABDOMINAL SURGERY"*

Not infrequently, when an abdominal operation is recommended for an infant or for a child, surprise is expressed by such a remark as, "I didn't know babies and children ever had such things," or doubt about the ability of the young to stand a surgical operation is indicated. So commonly are these ideas held that it has seemed wise to include some discussion of those conditions of the abdomen for which surgical treatment is desirable in the young.

The young differ from their elders in the frequency with which they are affected rather than in the types of their diseases. Thus, it has been stated correctly that the infant or child may present any of the surgical conditions recognized later in life, but that certain of them are very rare in the young and others are relatively common. The young differ also in their response to disease and may be prostrated seriously by an injury or infection sooner than adults would be. However, with appropriate treatment and management, their recuperative powers are tremendous, and their ability to heal and to repair damaged tissues is very great.

The first and most cheering point that I should like to make is that young persons are excellent surgical subjects, provided that the treatment is conducted by qualified surgeons, the hospital environment is adapted to the needs of infant and child, the anesthesia is well chosen and

*A "Green Lights to Health" broadcast given through Station WAAB by Dr. Henry W. Hudson, Jr., on December 6, 1941, and sponsored by the Public Education Committee of the Massachusetts Medical Society and the Massachusetts Department of Public Health.

administered skillfully, and the special instruments and equipment that may be necessary are available. Even a newborn baby will tolerate an abdominal operation of considerable magnitude. Indeed, a group of conditions seen in the newborn must be treated immediately by successful operation if the infant is to survive. These include certain errors in development prior to birth, which result in inability to take or to retain nourishment. Diaphragmatic hernia or so-called "upside-down stomach" and the several forms of obstruction of the intestinal tract are examples.

Not immediately but a few weeks after birth, a peculiar form of obstruction to the outlet of the stomach is seen fairly often. The fundamental cause is not known, but the effect is that the infant nurses hungrily, only to vomit all the feeding within a few minutes. Untreated, these patients lose or fail to gain weight and present a pitiful appearance of emaciation as they hungrily cry for the food they cannot retain. In hospitals interested in such patients, where large numbers are treated surgically, ninety-nine out of a hundred are permanently cured by operation on the stomach.

Somewhat later, at about the sixth or seventh month of life, the largest number of cases of intussusception or telescoping of the intestine into itself occurs. Although this serious surgical emergency may be seen at any age, curiously enough, it is much commoner in infants. Usually, there is sudden onset, with evidence of severe colicky pain causing the baby to draw his legs up, cry out and often become very pale. The pain comes at intervals with intervening periods of apparent well-being, and mucus and blood may later be passed with the stool. Promptly recognized and operated on within twenty-four hours of onset, practically all these patients may be saved, but when there is delay the loss of life mounts tragically with the duration of the attack.

At all ages, hernias or ruptures of several types are seen, and the young patient is no exception. Nonoperative treatment is not likely to result in cure, and the mere existence of a hernia constitutes a threat of serious complications, to say nothing of the inconvenience and discomfort that may be present. Some are inclined to temporize and delay operation for these patients, but there is no reason why a baby or child who is otherwise well cannot be cured surgically at almost any age. The end results of operation for hernia appear to be better when operation is performed in early rather than in adult life.

In general, one may say that the need for surgery results from one of several causes: errors in development, of which the digestive-tract obstructions and hernias are examples; injuries requiring surgical treatment — the abdomen may be the site of such an injury; automobile accidents, falls and injuries in schoolboy athletics that require operation for the repair of an injured organ or for the control of bleeding, although the relatively sheltered life of the young makes such accidents uncommon; and infections of the peritoneum or membrane lining the abdomen and covering the several organs. Thanks to the discovery of chemical methods of treatment within the last few years, there has been great improvement in the results of treatment, and many lives are saved that would otherwise have been lost.

Surgery may also afford the only chance of relief from tumors. Some of the tumors produce mechanical effects, which may be relieved dramatically by surgical removal. It will perhaps surprise my listeners to learn that young persons may be the victims of cancerous growths, but some of the most malignant tumors recognized are seen in the young. Certain of these are removed by abdominal operations, and the urgent need of early recognition and treatment cannot be overemphasized.

It sometimes happens that the most careful examination and x-ray and other studies do not suffice to determine a diagnosis of conditions affecting the abdomen and its contents. An exploratory operation to permit actual visualization and handling of the organs may be desirable. Such a procedure, if recommended, should not be a reason for dread or great concern. It is safe to say that a properly conducted exploration in itself is accompanied by very little risk to health, and much may be gained by the determination that conditions are normal or by finding and correcting an abnormality.

No discussion of the subject would be worth while unless emphasis was placed on a condition that is most commonly the reason for abdominal operation and unfortunately and unnecessarily occupies a very important place in the list of causes of death in the young. I say unfortunately and unnecessarily because, ideally, no child should suffer a long illness or have his life jeopardized by appendicitis. To reach the ideal, two things are necessary: prompt diagnosis and early operation. Study after study from surgical clinics throughout the country has demonstrated that with early diagnosis and operation there is almost no loss of life, but with delay and the development of complications the picture is very different. Studies from several large clinics interested in the surgical problems of early life have also demonstrated that, aside from the difficulties in diagnosis, there is nothing peculiar to the young that should result in a high death rate from appendicitis. The same excellent results can be obtained in the young that can be obtained in adults provided three conditions are fulfilled. These are as follows: no cathartics or laxatives for children with undiagnosed abdominal pain; prompt medical observation for any child who complains of abdominal pain for more than an hour or two; and prompt acceptance of the operation recommended if a diagnosis of appendicitis is made.

In my opinion, there is little place for the use of laxatives and cathartics, and they should never be employed for a young person with abdominal pain unless it is definitely known that appendicitis is not the reason for the pain. Such medication for a patient with appendicitis may well lead to early rupture of the appendix, which carries with it a number of very serious complications.

Appendicitis is a treacherous disease, particularly in the young. It may occur at any age, even in infancy, and, after the first few years of life, becomes increasingly frequent until the age of twenty to thirty. It is particularly treacherous in children for three reasons: because it is not thought of as a possibility; because it may be difficult to diagnose early; and because it often develops more rapidly in the young than in those who are older. It may occur coincidentally with or perhaps be related to certain infections, such as colds, sore throats, measles and chicken pox, and its early symptoms of abdominal pain and vomiting are the common symptoms of many acute infections in childhood. There is only one safe rule, and that is to regard the symptoms of abdominal pain and vomiting as possibly indicating appendicitis until competent medical opinion rules out this diagnosis.

Although most cases follow a pretty definite series of symptoms, there is still a wide variation that calls for careful thought and interpretation if a diagnosis is to be made before there are serious complications. Unfortunately, it is not possible to set forth a series of iron-clad rules to protect from disaster, but it is worth while to

point out the usual symptoms and to correct certain misconceptions that experience has shown to be prevalent.

There need not be previous attacks or premonitory symptoms. The best time for operation is early in the first attack. It is seldom, if ever, wise to wait and see if the attack will subside — occasionally it may, but the risk is too great to accept. Appendicitis cannot be "frozen out" by an ice bag; indeed, only surgical treatment need be considered. The existence of some other condition, such as a cold, measles or chicken pox, does not mean that the child does not also have appendicitis. The pain need not be severe, — frequently it is, and this is fortunate, since it usually results in attention to the abdomen, — but often the pain is annoying, grumbling and persistent rather than severe and excruciating, and occasionally there is no complaint of pain at all. There is usually very little fever, commonly between 99 and 101°F., but this is subject to variations from a normal level up to 103°F. Again, abdominal tenderness is usually but not always apparent on examination, generally in the right lower part of the abdomen; however, it may be elsewhere, and any tenderness anywhere in the abdomen is always very significant. Sometimes, the tenderness is evident only after the physician has made an examination of the rectum. Vomiting almost always occurs after the onset of pain, but may precede pain or may be totally absent. A count of the white blood corpuscles is usually desirable to establish the diagnosis, but may be unnecessary — this is a matter for the physician to decide.

Finally, if your physician recommends operation for your baby or child, accept his advice with the assurance that there are many good reasons for such operations, and that under proper conditions the risk is very slight, and negligible when compared with the risk of withholding operation.

MISCELLANY

CONSERVATION OF SCHOLARLY JOURNALS

In 1941, the American Library Association created the Committee on Aid to Libraries in War Areas, headed by John R. Russell, librarian of the University of Rochester. The committee is faced with numerous serious problems and hopes that American scholars and scientists will be of considerable aid in the solution of one of these problems.

One of the most difficult tasks in library reconstruction after World War I was that of completing foreign institutional sets of American scholarly, scientific and technical periodicals. The attempt to avoid a duplication of that situation is now the concern of the committee.

Many sets of journals will be broken by the financial inability of the institutions to renew subscriptions. So far as possible, they will be completed from a stock of periodicals being purchased by the committee. Many more will have been broken through mail difficulties and loss of shipment, while still other sets will have disappeared in the destruction of libraries. The size of the eventual demand is impossible to estimate, but requests received by the committee already give evidence that it will be enormous.

With an imminent paper shortage, attempts are being made to collect old periodicals for pulp. Fearing this possible reduction in the already limited supply of scholarly and scientific journals, the committee hopes to enlist the co-operation of subscribers to the *Journal* in preventing the sacrifice of this type of material to the pulp demand. It is scarcely necessary to mention the appreciation of foreign institutions and scholars for this activity.

Questions concerning the project or concerning the value of particular periodicals to the project should be directed to Wayne M. Hartwell, Executive Assistant, Committee on Aid to Libraries in War Areas, Rush Rhees Library, University of Rochester, Rochester, New York.

RÉSUMÉ OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JANUARY, 1942

Diseases	January 1942	January 1941	Five-Year Average*
Anterior poliomyelitis	2	0	1
Chicken pox	2275	1574	1861
Diphtheria	14	9	20
Dog bite	591	511	561
Dysentery, bacillary	6	3	13
German measles	130	63	60
Gonorrhea	357	263	376
Measles	1018	1887	1885
Meningitis, meningococcal	11	3	6
Meningitis, other forms	9	6	—
Mumps	2231	836	701
Paratyphoid infections	7	5	2
Pneumonia, lobar	390	1052	733
Scarlet fever	1401	586	819
Syphilis	417	296	414
Tuberculosis, pulmonary	222	269	250
Tuberculosis, other forms	19	27	26
Typhoid fever	8	4	6
Undulant fever	1	5	4
Whooping cough	1111	1076	1084

*Based on figures for preceding five years.

Geographical Distribution of Certain Diseases

Anterior poliomyelitis was reported from: Pittsfield, 2; total, 2.

Diphtheria was reported from: Billerica, 1; Boston, 3; Chelsea, 1; Fall River, 4; Lowell, 2; Shrewsbury, 1; Somerville, 1; Springfield, 1; total, 14.

Dysentery, amebic, was reported from: Marblehead, 1; total, 1.

Dysentery, bacillary, was reported from: Camp Edwards, 1; Salem, 1; Tewksbury, 3; Waltham, 1; total, 6.

Encephalitis, infectious, was reported from: Fort Devens, 1; Wellesley, 1; total, 2.

Lymphocytic choriomeningitis was reported from: Winchester, 1; total, 1.

Malaria was reported from: Cambridge, 1; total, 1.

Meningitis, meningococcal, was reported from: Amesbury, 1; Beverly, 1; Boston, 1; Cambridge, 1; Danvers, 1; New Bedford, 2; Norwood, 1; Springfield, 2; Winchendon, 1; total, 11.

Meningitis, other forms, was reported from: Boston, 5; Cambridge, 1; Greenfield, 1; New Bedford, 1; Reading, 1; total, 9.

Paratyphoid infections were reported from: Boston, 1; Gardner, 2; Malden, 1; Quincy, 2; Reading, 1; total, 7.

Septic sore throat was reported from: Barnstable, 1; Boston, 4; Burlington, 1; Cambridge, 3; Fall River, 1; Falmouth, 1; Gloucester, 1; Hanover, 1; Medford, 1; Newburyport, 1; Westford, 1; total, 16.

Tetanus was reported from: Fall River, 1; Springfield, 1; total, 2.

Trachoma was reported from: Boston, 1; total, 1.

Trichinosis was reported from: Cambridge, 1; Lakeville, 1; total, 2.

Typhoid fever was reported from: Bellingham, 1; Boston, 4; Gardner, 1; Waltham, 1; Worcester, 1; total, 8.

Typhus fever was reported from: Arlington, 1; total, 1.

Undulant fever was reported from: Boston, 1; total, 1.

Mumps continued to show a record high incidence for the seventh consecutive month.

Chicken pox, meningococcal meningitis, German measles, scarlet fever, typhoid fever and whooping cough were reported above the five-year averages.

Bacillary dysentery, diphtheria, measles, pulmonary tuberculosis, other forms of tuberculosis and undulant fever were reported below the five-year averages.

Lobar pneumonia showed a record low incidence for the second consecutive month.

The focus for animal rabies that has been noted in the northeastern section of the State is still active in Middlesex County, cases having been reported from Burlington, Woburn, Danvers and Tewksbury.

REPORT OF MEETING

NEW ENGLAND PATHOLOGICAL SOCIETY

A meeting of the New England Pathological Society was held on October 16, at the Boston Lying-in Hospital. Dr. Earle B. Clarke presided.

The first paper, "Morphologic Findings from Endometrial Biopsy from 100 Cases of Bleeding during the First Trimester of Pregnancy and from 34 Cases of Puerperal Uterus," was presented by Dr. Robert N. Rutherford. Application of the technic of endometrial biopsy to the problem of bleeding in the first trimester of pregnancy in 100 consecutive bleeding cases in the Out-Patient Department of the Boston Lying-in Hospital has evolved as a simple, safe, quick procedure for the detection of the inevitability of abortion. This is based on the high incidence of pathologic ova in which the embryo is absent or very defective and which form the bulk of spontaneous abortions in the first trimester. The embryos in such specimens tend to die or cease developing, on an average, six weeks before actual extrusion at the usual "lamentable miscarriage." Fetal death or lack of fetal development initiates thrombosis, necrosis and hemorrhage within the decidua and beneath the placental plate, probably on the basis of slow withdrawal of the pregnancy corpus-luteum hormone. These changes are irreversible, and are easily recognizable as characteristic, even on frozen section. Such a finding precludes any need for hormone treatment or restriction of the patient's activities, for Nature is ridding the uterus of defective human materials. The procedure carries no danger to a normal pregnancy up to the fourteenth week. Its diagnostic accuracy is very high. In the 100 cases so studied, 50 were associated with pathologic ova, 42 with defective implantation or defective placental development and 2 with ectopic pregnancy; 6 patients were not pregnant. Progesterone in massive doses was of no value in either major problem — defective fetal development or defective implantation, with or without placental or appendage fault.

The technic has also been used to study the regeneration of the uterine mucosa following normal full-term delivery and spontaneous abortion. It has been demonstrated in 25 post-partum cases that regeneration is complete within two or three weeks following delivery, that ovulation takes place about six weeks after delivery, but that lactation inhibits ovulation for varying periods. Following spontaneous abortion, regeneration is complete in the ideal case in five to seven days, ovulation occurring fourteen days after a curetted abortion. Failure to curette, heavy preabortion progesterone therapy or retained placental fragments will not delay regeneration, but will delay resumption of the normal ovarian cycle. Routine immediate postabortion curettage is recommended. Subsequent impregnation can take place within two weeks after abortion, and curettage is recommended as a time-saving procedure in difficult sterility problems.

In the discussion, Dr. Somers H. Sturgis stated that Dr. Rutherford had shown that a biopsy of the lower uterine segment can be done without precipitating abortion. It must be emphasized, however, that such a result cannot always reasonably be expected in less experienced hands. The procedure certainly is never justified in the diagnosis of normal pregnancy. Interpretation of the material is as significant as the method of taking the biopsy. It would take a great deal of confidence for most physicians to empty a uterus on the frozen-section findings without waiting for permanent sections. However, it is possible to diagnose a nonviable fetus on frozen section of the decidua alone. Dr. Sturgis entirely agreed with Dr. Rutherford's conclusions regarding the futility of progesterone treatment of bleeding cases by calling attention to the uselessness of giving this hormone to cases that already show irreversible, degenerative decidual changes. He wondered, however, whether it might not be worth while to give 10 mg. of this hormone as a routine, prior to taking the biopsy. This might render the uterine muscle temporarily refractory and thus give a certain amount of protection to cases with an unaffected fetus. Sometimes, a biopsy initiates uterine cramps, and if this protection were used, an occasional calamity might be averted.

With respect to the second part of the paper on the regeneration of uterine mucosa following abortion and delivery, Dr. Sturgis stated that Dr. Rutherford deserves a great deal of credit for his careful histologic examination of daily specimens of post-partum endometrium. So far as he knew, no such study had previously been performed to throw light on the state of the endometrium during regeneration after spontaneous abortion and after normal delivery in both lactating and nonlactating mothers. A comparison of his results in these three groups reveals that endometrial regeneration after spontaneous abortion and curettage is complete in about one week, with evidence of ovulation by the fourteenth day and normal menses on the twenty-eighth day. Such an immediate return to the normal cycle is not unexpected. It may be ascribed to an immediate release of the follicle-stimulating hormone of the pituitary gland, previously inhibited by the high titer of estrogens produced by the products of conception. A similar immediate release follows estrogen withdrawal under other circumstances. For example, at the Massachusetts General Hospital, Dr. Sturgis and his colleagues have inhibited the pituitary gland and suppressed the ovarian cycle for about three weeks in a large group of patients with dysmenorrhea. It is noteworthy that in these patients, as in women who have spontaneously aborted and who have been curetted, ovulation apparently occurs in about two weeks, and a normal period almost invariably about twenty-eight days after the estrogen has been abruptly withdrawn. On the other hand, Dr. Rutherford has noted that this prompt pituitary reactivation, with consequent ovulation, does not necessarily occur if curettage is not performed after spontaneous abortion. In one of his cases, in which all the products of conception were identified so that no curretting was done, a biopsy on the thirty-fifth day still showed regressing decidua. The patient apparently had not ovulated. Dr. Sturgis was tempted to speculate on the possible role of retained decidua on the storage or metabolism of estrogen and its possible effect on the pituitary.

In the other two groups of patients, — the nonlactating

and the lactating mothers, — Dr. Rutherford finds regeneration complete in about twelve days. This interval is what one might expect in comparison with that of seven days after abortions under three months. In the nonlactating mothers, as well as in some that lactate, ovulation did not occur in his cases for six weeks. The exact role of the lactogenic hormone in suppressing gonadotropic activity is not precisely known. Failure to lactate, however, does not necessarily indicate a subnormal production or absence of the lactogenic hormone. The trouble may lie in unresponsive breast tissue. It seems likely that production of lactogenic hormone post partum in some way represses the output of follicle-stimulating hormone for three to four weeks. If the mother does not or cannot nurse her child, the gonadotropic activity of the pituitary gland is released at that time, as evidenced by ovulation at about the fifth or sixth week in some cases. In many lactating mothers who continue nursing, however, the stimulus from suckling in some way continues the output of lactogenic hormone and the consequent repression of follicle-stimulating hormone. Dr. Sturgis considered the chief value, perhaps, of Dr. Rutherford's work to be in presenting clear evidence that, during the period of lactation amenorrhea, the endometrium is proliferative — in a relatively resting stage. Amenorrhea at this time, then, is associated neither with persistence of the corpus luteum of pregnancy nor with any new corpus luteum maintained by lactogenic hormone. A regenerated endometrium remains resting until the pituitary gland finally breaks through the inhibition of the estrogens of pregnancy and of the lactogenic hormone, and not till then does the normal four-week cycle of proliferation and secretion start.

The second paper, "Bilateral Cortical Necrosis of the Kidney: A report of two cases with some observations on the pathogenesis and evolution of the renal lesion," was presented by Dr. Walter H. Sheldon.

Two cases of symmetrical cortical necrosis of the kidney following toxic separation of the placenta were presented. The renal lesion consisted of necrosis in the wall of the afferent arteriole at the point where the vessel enters the glomerulus. This necrosis, which in most cases was associated with thrombosis and followed by retrograde extension in the intralobular and interlobar arteries, led to ischemic necrosis of the kidney. Similar lesions were found in the anterior lobe of the pituitary gland, in the pituitary stalk and in the tuber cinereum, as well as in the cecum and adrenal gland.

Dr. Foster Kellogg, commenting on the clinical aspects of cortical necrosis of the kidneys, emphasized the difficulty in making the diagnosis clinically. He reviewed a series of cases with oliguria or anuria in association with toxemia of pregnancy or premature separation of the placenta, and concluded that if a patient with premature toxic separation fails to pass much urine in the first two or three days it does not signify definitely that she has cortical necrosis. It is perhaps better to force fluids and go on the assumption that she does not have cortical necrosis and may live, rather than to assume that she has cortical necrosis and is bound to die.

Dr. Richard Wadsworth stated that in a recent report he observed degenerative changes in the hypothalamus following sclerosis of the anterior lobe of the pituitary gland, in addition to lesions in the corpus callosum. He asked whether any degenerative cell changes were seen in either the optic or supraoptic nuclei of the hypothalamus, but Dr. Sheldon replied that he had looked specifically in these regions and found none.

Dr. Sheldon's remarks about the limits and distribution of the infarcted areas in the pituitary gland interested Dr. George Wislocki, who stated that the areas of infarction corresponded to the distribution of the superior hypophyseal arteries, — as investigated by him in the macaque monkey, — including the median eminence of the tuber cinereum, the pituitary stalk and the anterior lobe. The remainder of the tuber cinereum and the posterior lobe showed no infarction because, in Dr. Wislocki's opinion, their blood supplies derive from other sources, namely, from hypothalamic branches independent of the pituitary gland, and from the inferior hypophyseal arteries. He suggested that when infarction of the stalk occurs, one should anticipate eventual damage to the hypothalamus-hypophyseal tracts traversing the stalk, with related symptomatology.

The third paper, "Relation of Ovarian Stromal Hyperplasia and Thecoma of the Ovary to Endometrial Hyperplasia and Carcinoma," by Drs. George V. Smith, Lent C. Johnson and Arthur T. Hertig, was read by Dr. Johnson. Changes occurring in nonfollicle-bearing, postmenopausal ovaries appear to be frequently associated with hyperplastic, bleeding endometria. These changes are characterized by masses of dense, well-vascularized, stromal tissue in either the cortex or the medulla of the ovary, with a tendency to form whorls. Some of the stromal cells along capillaries in these whorls become large, fat-containing polyhedral cells and look like cells of the theca interna. To these changes, the term "stromal hyperplasia" has been given. When large numbers of such cells form a nucleus, there tends to be some infiltration of lymphocytes and macrophages in the area, associated at times with cholesterol-like slits. At such times, foreign-body giant cells surrounding the cholesterol slits make their appearance. To these focal collections, the term "cortical granulomas" has been given. As both stromal hyperplasia and cortical granulomas pass the peak of their anatomic activity, collagen is laid down, and finally only a nest of whorled, hyalinized fibrous tissue remains. The almost constant association of these lesions with hyperplastic bleeding endometrium suggests that there may be a more than coincidental relation between the fat-cholesterol slits and estrogen production.

These changes are very similar to the whorling, vascularity, fat deposition and finally collagen deposition seen in thecomas, and in mixed theca-granulosa-cell tumors. There is also a close parallel between the polyhedral theca-interna-like cells in these lesions and similar cells in the theca-granulosa-cell group of tumors. Of such tumors seen at the Free Hospital for Women through 1935 and reviewed by Dr. Smith, 16 per cent were associated with carcinoma of the uterus. In a paper recently published, he observes that of 180 cases of postmenopausal carcinoma of the uterus during the same period, 87 per cent were associated with excessive amounts of ovarian stromal activity, as judged by the quantity of whorled, vascular, stromal tissue, cortical granulomas and polyhedral theca-interna-like cells. This degree of stromal ovarian activity is much greater than that in a series of ovaries from procidentia patients over two years past the menopause who had had a normal menstrual history and no postmenopausal bleeding. Thus, there appears to be anatomic evidence of hyperestrinism in the ovary, in the form either of tumor or of evidence of increased stromal activity — in many cases of carcinoma of the uterus.

The discussion was opened by Dr. Smith, who stated that he was first impressed with hyperplasia of the stromal or thecal cell about six years ago, when combing the

pathological files of the Free Hospital for Women for granulosa-cell tumors and cystadenofibromas. During this review, it became evident that the cystadenofibromas were associated with postmenopausal bleeding and endometrial proliferation, although of a degree not so marked as that in cases with granulosa-cell tumors. Until two years ago, however, thecal-cell hyperplasia was to him only an interesting observation. No correlation with other pelvic lesions was evident. At this time, he began reviewing pathology for a paper on cancer of the endometrium, and the frequency of thecal-cell hyperplasia in cases with this type of cancer was immediately apparent. Eighty-seven per cent (156 cases) of the postmenopausal ovaries (180 cases) had what was interpreted as slight to marked thecal-cell activity. Sections of endometrium were available from 62 of this group, and 48, or 77 per cent, showed more or less proliferation, mostly less. Dr. Smith was unable to correlate the amount of thecal-cell hyperplasia with the amount of endometrial activity. Endometrial hyperplasia has for some years been considered a possible forerunner of later endometrial cancer. This idea received support from the findings, by Dr. Smith and others, of a relatively frequent association between granulosa-cell tumors and carcinoma of the endometrium. About one fifth of his patients with granulosa-cell tumors after the menopause also had endometrial cancer. Conversely, of 180 postmenopausal patients with carcinoma of the endometrium seen before 1936 whose ovaries had been sectioned, 5, or 2.7 per cent, had granulosa-cell tumors. If he includes those with marked diffuse thecal-cell hyperplasia and those with cystadenofibroma, the percentage of cases of endometrial carcinoma with unmistakable microscopic ovarian activity becomes 8. Compared with the control group of postmenopausal ovaries from cases of procidentia, which Dr. Johnson and he examined together, 90 per cent of the group with carcinoma of the endometrium had significant microscopic ovarian activity, ranging from slight thecal-cell hyperplasia to actual granulosa-cell tumor. He would be more excited about the former if the available sections of endometrium had shown more convincing evidence of estrogenic stimulation. Perhaps lesser grades of thecal-cell activity yield subthreshold amounts of estrogenic steroid for the endometrium. Perhaps, also, it is wrong to assume that thecal-cell activity indicates the production of only an estrogenic steroid. For the present, all that can be submitted is that, based on microscopic study, cessation of menstruation does not necessarily mean that the ovaries have ceased functioning.

The last paper, "Observations on a Series of Early Normal and Abnormal Human Ova Obtained prior to the First Missed Menstrual Period," by Drs. Arthur T. Hertig and John Rock, was presented by Dr. Hertig. A series of eight early human ova, — four pathologic and four normal, — discovered incidentally in uteri removed surgically before the first missed menstrual period, was reported.

The ovulation age of the normal ova varies from eleven to sixteen days, and that of the pathologic ova from twelve to thirteen days. The normal specimens, including the youngest human ovum thus far observed, encompass the developmental period just before and just after the formation of the chorionic villi. The uteroplacental circulation has just begun and consists of a series of large anastomosing sinusoids, developed from the endometrial capillaries, whose finer branches are tapped directly by the eroding trophoblast, thereby flooding the trophoblastic lacunas (future intervillous spaces). Hemorrhage into the surrounding endometrium is a constant feature in normal as well as in abnormal cases. Recent hemorrhage — variable in amount — is also free in the uterine cavity in both normal and abnormal cases, and arises from the defect in the endometrium created by the embedding ovum.

The significance of the pathologic ova lies in the fact that from them can be evaluated certain factors in the pathogenesis of spontaneous abortion. In all four of these specimens, the ovum itself is definitely defective, either because of lack of an embryo or because of some local or general defect in the trophoblastic development. Detailed studies are in progress to determine whether the environment of these ova is significantly different from that of the four normal ova and hence could have caused the ovular defect, or whether the latter is present at such an early stage of development in spite of a normal environment.

In the discussion, Dr. Wislocki emphasized the importance of Dr. Hertig's preparations, which, he believes, realize the hope of embryologists of discovering and studying the earliest stages of human development. Through the efforts of Drs. Hertig and Rock, this goal is well on its way to being attained. Their series contains perfect implantation stages of the eleventh and twelfth days, and since the free blastocyst presumably attaches to the endometrium on the ninth day (as in the macaque), it is anticipated that this small but critical gap in the knowledge of implantation of the human egg will soon be filled.

BOOK REVIEWS

Diseases of the Thyroid Gland, Presenting the Experience of More Than Forty Years. By Arthur E. Hertzler, M.D. 4°, cloth, with 354 illustrations, and 2 color plates. New York: Paul B. Hoeber, Incorporated, 1941. $8.50.

In his preface, the author states that this book is "in no wise a treatise on the thyroid gland." It is merely a record of his studies, which now extend "over a period of nearly fifty years."

The style is unorthodox but entertaining. The plan of the book, as set forth in the "Table of Contents," the system of classification of goiters, and the illustrations are excellent. The text is confused and confusing, repetitious and sometimes circular in reasoning. Many of the assertions made invite dispute — for example, "Of what the thyroid gland has to do once the body is developed we know less than nothing." It seems to the reviewer that at least something is known about the function of the thyroid gland in the adult organism.

The genesis of this book, the author says, was the criticism leveled by pathologists at his theory of the toxic nature of myxedema. It seems to the reviewer that a not very successful attempt to refute these critics is the chief purpose of this book.

There is much teleologic reasoning and argument by analogy with commonplace mechanisms. Total thyroidectomy is advocated for all goiters, and the claim that myxedema is relieved by such an operation is put forward. There is much discussion of physical changes in the colloid (based exclusively on staining reactions), which leads to disturbed cellular functions. A thesis is maintained for the existence of a degenerative state of the thyroid gland in addition to the "toxic" factor in the production of "goiter heart," a term that is used quite loosely throughout.

The author's plea to regard the basal metabolic rate as an adjunct in diagnosis rather than as an absolute expression of thyroid function is well taken, but is so distorted in its emphasis as to lead to a dangerous disregard of a

procedure that, when competently interpreted, has proved its utility in the general run of cases.

The sections on the surgical pathology of goiter emphasize the lack of uniformity of histologic states as correlated with the clinical picture; the importance of the stage of the disease is appreciated in this relation, and the fact that large cancers grow from small adenomas is reiterated.

The author lays great stress on the relief of such symptoms as tachycardia, nervousness and weight loss by the removal of nontoxic goiters, but he cites a case in which such symptoms were relieved by the removal of a large lipoma of the neck. This case throws some doubt on the relation between relief of these symptoms and thyroidectomy in his cases of nontoxic goiter.

Health and the Doctors. In: *Propaganda Analysis: A bulletin to help the intelligent citizen detect and analyze propaganda.* Vol. IV, Number 11. 4°, 16 pp. New York: Institute for Propaganda Analysis, Incorporated, 1941.

This issue in the series of pamphlets on propaganda analysis is concerned with the efforts of organized groups to influence the public in the type of medical care to be selected. The philosophies, propaganda methods and motives of the various groups are opposed and analyzed. The arguments of the organizations sponsoring outright socialization and state control are presented more favorably than those of any other, and one gains the impression that the editor, wittingly or unwittingly, has himself subtly expressed a viewpoint in support of socialized medicine. The pamphlet is worth reading by the critical student interested in this subject.

Fatal Partners: War and disease. By Ralph H. Major, M.D. 8°, cloth, 342 pp., with 13 illustrations. New York: Doubleday, Doran and Company, Incorporated, 1941. $3.50.

War and disease have always gone hand in hand. Dr. Major has gone through the records of history and brought into the pages of a single volume the chief aspects of medical interest in relation to military combat. The story is an interesting one. Unfortunately, the style in which the book is written takes away from the pleasure of reading; there is evidence of haste in compilation. To the reviewer, the illustrations often seem to be of slight value, and the book cannot be highly recommended on this account. Although the author presents much that is of value, he has not eliminated considerable irrelevant material.

Vitamin K. By Hugh R. Butt, M.D., M.S. in Medicine, and Albert M. Snell, M.D., M.S. in Medicine. 8°, cloth, 172 pp., with 39 illustrations, and 14 tables. Philadelphia: W. B. Saunders Company, 1941. $3.50.

The problems posed by the discovery of the existence and probable importance of vitamin K constituted a challenge that was met forcefully and adequately. This book represents the tremendous strides that can be made in modern research within the compass of a few years once the impetus has been given. As a result of this co-ordinated experimental and clinical research, practical results of great, lifesaving value have materialized. The first portion of the book is devoted to the historical aspects involving the initial studies in hemorrhagic disease of chicks. Then follows a discussion of the chemistry of vitamin K and, finally, of the clinical studies and applications. Conditions unassociated with vitamin K deficiency and hence not influenced by its use are also considered. This small volume presents an excellent summary of a subject that should be familiar to all physicians. An excellent bibliography is appended.

Pathology of the Oral Cavity. By Lester R. Cahn, D.D.S. 8°, cloth, 240 pp., with 165 illustrations. Baltimore: The Williams and Wilkins Company, 1941. $5.50.

Half of this work is devoted to a description of the pathology of the teeth and jaws, and the remainder to the common lesions involving the soft tissues of the oral cavity.

The book, as its title indicates, is truly a treatise on the pathology of the oral cavity and is especially useful in correlating the pathologic tissue changes with the clinical findings in oral lesions.

There is an abundance of illustrations, a few of which are in color. The histopathological plates are especially clear, and the bibliography is brought up to date.

On the whole, the descriptive material is too brief for this to be regarded as a textbook, but the work can be recommended as a reference to the dental student, to the scientifically minded practitioner of dentistry, and to physicians interested in oral disease.

Lymphatics, Lymph, and Lymphoid Tissue: Their physiological and clinical significance. By Cecil K. Drinker, M.D., D.Sc., and Joseph Mendel Yoffey, M.Sc., M.D., F.R.C.S. (Eng.). 8°, cloth, 406 pp., with 50 illustrations and 45 tables. Cambridge, Massachusetts: Harvard University Press, 1941. $4.00.

The reviewer considers this a work of unique importance that collects material from varied sources to produce a comprehensive and valuable description of the present-day physiology of the lymphatic system. The authors have personally added a great deal to the knowledge of lymphatics and lymph, and are admirably qualified to produce this monograph, in which their own work and that of others are critically evaluated. They deserve particular commendation for carefully separating fact from speculation in the application of their material.

The book should be read by every physician desirous of keeping abreast of significant advances in medicine. Although the biologist and teacher will be fascinated by the basic anatomy and physiology presented, the work should prove at least as interesting and valuable to the practitioner of medicine.

Wide applications of the knowledge of the lymphatic apparatus are presented. The hematologist, for example, will be interested in the discussions of the production and loss of lymphocytes, and the bacteriologist in the material on the transport of viruses by way of the lymphocytes; the internist and surgeon will both find valuable matter on edema and inflammation.

Sulfanilamide and Related Compounds in General Practice. By Wesley W. Spink, M.D. 8°, cloth, 256 pp. Chicago: The Year Book Publishers, Incorporated, 1941. $3.00.

Since the introduction of the sulfonamides as a new chemotherapeutic approach to the treatment of infection, a veritable flood of studies has appeared. This small volume endeavors to summarize the principal facts gleaned from the literature. Appropriate attention is directed to the untoward reactions that may be associated with the various chemicals. The inclusion of sulfadiazine brings the book fairly well up to date. Those seeking a brief but adequate survey of the sulfonamides will profit from this book.

(Notices on page viii)